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Cardiomyocyte autophagy: metabolic profit and loss

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Abstract

Cardiovascular disease remains the leading cause of morbidity and mortality worldwide, even despite recent scientific and technological advances and comprehensive preventive strategies. The cardiac myocyte is a voracious consumer of energy, and alterations in metabolic substrate availability and consumption are hallmark features of these disorders. Autophagy, an evolutionarily ancient response to metabolic insufficiency, has been implicated in the pathogenesis of a wide range of heart pathologies. However, the precise role of autophagy in these contexts remains obscure owing to its multifarious actions. Here, we review recently derived insights regarding the role of autophagy in cardiac hypertrophy and heart failure, highlighting its effects on metabolism.

Keywords

Cardiomyopathy; Cardiac remodeling; Cardiac hypertrophy; Heart failure; Metabolism

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide [1]. In 2008, CVD accounted for 1 in every 3 deaths in the United States, posing a tremendous burden on our society, healthcare system, and economy [2]. The total cost (direct and indirect) of CVD in the US was \$445 billion in 2008, and this cost is projected to rise to \$1.09 trillion by 2030 [3]. By then, over 40 % of the US population is projected to have some form of CVD.

Many forms of heart disease progress inexorably to a state of circulatory insufficiency, where the metabolic needs of the body cannot be met by the heart and vasculature. This highly prevalent syndrome, termed heart failure, has remained the single leading discharge diagnosis in Medicare for a number of years running, and this sad reality is expected to persist and worsen into the foreseeable future [2].

High blood pressure constitutes the single most prevalent and important risk factor for heart failure; approximately 75 % of heart failure cases have antecedent hypertension [2]. According to Grossman's stress-adaptation hypothesis, augmented mechanical stress imposed by hypertension-induced pressure overload transduces a signal that stimulates proliferation and recruitment of cardiomyocyte sarcomeres in parallel with consequent increases in wall thickness [4]. Based on Laplace's law, ventricular wall stress is proportional to both ventricular pressure and cavity radius and inversely proportional to ventricular wall thickness [5]. Thus, increases in wall thickness tend to diminish wall stress and thereby lessen oxygen demand. Under conditions of persistent pressure overload, however, the concentric hypertrophic state of the myocardium slowly progresses to a state of decompensation and clinical heart failure. The underlying mechanisms governing this transition from adaptive hypertrophy to maladaptive failure remain poorly understood.

As a post-mitotic cell, cardiomyocytes retain minimal, if any, proliferative capacity in the adult stage [6]. Rather, myocardial growth and increases in mass derive virtually exclusively from cardiomyocyte enlargement. This process, in turn, is determined by the balance of protein synthesis and protein degradation. In the setting of pressure stress, protein synthesis predominates, culminating in a hypertrophic phenotype [7]. Hypertrophic remodeling, however, is not a simple process of addition of new sarcomeres. Rather, this highly dynamic cellular remodeling response involves intricate coordination of de novo protein synthesis, organelle formation, protein degradation, and organelle breakdown. Imbalances between anabolic and catabolic mechanisms likely are important contributors to cardiovascular pathology.

The ubiquitin proteasome system (UPS) is responsible for degradation and recycling of the majority of unneeded proteins. Accumulating evidence suggests that the UPS is significantly suppressed during states of pressure overload [8, 9]. As a result, intracellular levels of ubiquitinated proteins are elevated in hypertrophic hearts. Thus, impaired UPS activity may contribute to the dysregulated balance between protein synthesis and protein degradation in pathological cardiac remodeling.

Another major catabolic mechanism is autophagy, an evolutionarily conserved mechanism of recycling of long-lived proteins and clearance of defective organelles [10]. Basal autophagy is critical for cellular homeostasis and survival [11]. In addition to this fundamental housekeeping function, autophagy also plays important roles in metabolism by replenishing energy substrates and governing mitochondrial number and quality control [12]. It has long been appreciated that cardiac hypertrophy and heart failure are accompanied by extensive metabolic remodeling [13–16]. In each of these states, autophagic activity is induced, and recent studies have begun to explore the role of this autophagic response in the metabolic shifts of cardiac hypertrophy and failure [17–19]. Here, we review the role of autophagy in the plasticity responses of cardiac hypertrophy and failure, placing emphasis on metabolic regulations.

Autophagy, a self-eating process

Autophagy is an ancient and near-ubiquitous process of delivery of cytoplasmic materials, including proteins and organelles, to lysosomes for degradation [20]. Based on differences in mechanism and function, autophagy has been divided into three types: microautophagy, macroautophagy and chaperone-mediated autophagy. Macroautophagy is the most common form of autophagy and hereafter will be referred to as autophagy.

Autophagy is a dynamic and highly regulated process (Fig. 1). A number of autophagy-related (ATG) proteins are recruited to form regulatory protein/lipid complexes which govern the processes of phagophore nucleation and expansion, autophagosome fusion with a

lysosome, and ultimately membrane retrieval [21]. For example, the ATG1/ATG13 kinase complex controls the induction of autophagy. Upon nutrient starvation and/or growth factor deprivation, the dissociation of the TOR kinase complex from ATG1/ATG13 promotes activation of ATG1 kinase activity, which in turn triggers autophagy induction. The class III PI3K complex, comprising Beclin 1, VPS15, and VPS34, triggers the formation of an isolation membrane from membrane harvested from the endoplasmic reticulum, plasma membrane, or mitochondria. Following nucleation, two ubiquitin-like protein/lipid conjugation systems, ATG12 and ATG8 (LC3), promote the expansion of the isolation membrane, engulfment of cytoplasmic materials, and formation of the double-membrane autophagosome. After fusion with the single membrane lysosome to create an autolysosome, the inner membrane of the autophagosome, along with engulfed materials, is degraded by hydrolases and proteases delivered by the lysosome. Ultimately, the degraded contents are released into the cytoplasm via permeases. Finally, ATG9 and ATG18 mediate the retrieval of components of the autolysosome [10].

Autophagy is critical for cell survival during states of energy crisis. However, due to the partially nonselective nature of cargo selection, excess degradation of essential components can be detrimental and may possibly even provoke cell death [22]. In light of the diverse roles of autophagy—required for survival, critical for stress responsiveness, and yet harmful in some contexts—it is not surprising that autophagy is governed by a complex, interlacing regulatory circuitry.

Autophagy, a housekeeping process

One of the most important functions of autophagy is degradation of long-lived proteins and defective—potentially harmful—organelles. Deficiency of basal autophagy has been implicated in heart disease [11, 17, 23]. For example, Danon disease (also known as lysosomal glycogen storage disease with normal acid maltase) is marked by moderate to severe cardiac hypertrophy, heart failure, vacuolar myopathy, and mental retardation [24, 25]. LAMP2, a principal lysosomal membrane protein, is mutated in patients with Danon disease [26]. In vivo studies using LAMP2-deficient animals confirmed that LAMP2 mutation can cause abnormal autophagosome accumulation in multiple organs including the heart [27]. Further, the half-life of long-lived proteins is significantly prolonged in LAMP2-deficient cells. At the ultra-structural level, cardiomyocytes become engorged with large numbers of autophagosomes containing undigested cytosolic material [27]. LAMP2-null mice manifest profound cardiac hypertrophy and diminished contractile function. Moreover, it has been suggested that LAMP2 mutation may be a clinically unrecognized risk factor for cardiac hypertrophy in children [28].

Autophagy plays an important role in protecting the heart from protein aggregation-induced cardiomyopathy. Mutation of the highly expressed chaperone protein β -crystallin provokes a severe and progressive form of heart failure in affected cohorts. A transgenic mouse model harboring the same R120-mutated β -crystallin recapitulates many features of this disorder and serves as an informative model of protein misfolding-induced cardiac pathology. We reported that cardiomyocyte autophagy is potently induced in these animals, consistent with a requirement for the activation of pathways to eliminate toxic misfolded proteins [29]. Moreover, suppression of autophagic activity in this model exacerbated the accumulation of protein aggregates and provoked deteriorations in cardiac function, again consistent with a beneficial role of autophagic flux in this disorder. These findings were recently confirmed and extended by Robbins and colleagues in tissue culture studies [30]. They found ATG7 overexpression augmented autophagic activity, and β -crystallin R120G aggregates were dose dependently reduced. Conversely, in the absence of ATG7, cytotoxicity was exacerbated. Collectively, these results indicate that basal autophagic flux is fundamental to

the maintenance of cellular homeostasis and to the normal functioning and welfare of cardiomyocytes.

Autophagy in starvation

Nutrient deprivation is a major physiological stimulus of autophagy. Starvation-induced autophagy plays indispensable roles in replenishing nutrients for ATP generation, thereby promoting survival. As the heart consumes extremely large amounts of energy on a never-ending basis, it is not surprising that autophagy is robustly induced in the starved heart [31]. For example, in the immediate perinatal phase of life, the newborn faces an abrupt energy crisis; nutrient supply via the maternal-fetal circulation is interrupted, and autophagy is dramatically activated in response [32]. Abrogation of that autophagic response by ATG5 inactivation provokes depletion of respiratory substrates, and cardiac abnormalities become apparent shortly after delivery. Autophagy is dramatically stimulated in cardiomyocytes of mice subjected to short-term nutrient deprivation [33, 34], findings which were confirmed in neonatal and adult cardiomyocyte cultures [33, 35]. Suppression of autophagy by ATG5 or LAMP2 knockdown triggers necrotic cell death, whereas enhancing autophagy using rapamycin improves cell survival.

Similar to many processes in biology where a delicate balance is required to maintain homeostasis, overactivation of autophagy can be maladaptive. We have found that incubating nutrient-deprived cardiomyocytes with IGF-1, a pro-survival growth factor, potently enhances mitochondrial biogenesis, suppresses autophagy, and increases cell viability [36]. Similarly, inhibiting autophagy using salivianolic acid B is protective of cardiomyocytes from starvation-induced cell death [37]. At a mechanistic level, starvation of a cardiomyocyte may increase DNA damage by autophagy-mediated degradation of 8-oxoguanine DNA glycosylase, an enzyme critically involved in base excision repair [38]. Collectively, these studies suggest that even though autophagy as an early-phase response to starvation is adaptive and beneficial, prolonged starvation may provoke excessive autophagy which can engulf and eliminate essential cellular constituents, promoting cell death. Thus, fine-tuned regulation of autophagy in starvation is critical to the maintenance of normal cell and organ function.

Autophagy in cardiac hypertrophy

Autophagy is potently induced in heart by increases in afterload (reviewed in [17–19]). Early studies by Pfeifer and colleagues scored autophagic vacuole changes in aortic constriction-induced cardiac hypertrophy in rats [39]. This work uncovered significant decreases in vacuole abundance in the early phases of hypertrophic growth (7 days post-operation), findings which were interpreted to reflect a reduction in autophagic activity. However, we now know that the phenomenon reported by Pfeifer and colleagues may actually reflect an increase in autophagic flux leading to diminution in autophagosome number within the cell. Our group reported that a prominent autophagic response can be detected as early as 24 h post-aortic banding with especially robust activity occurring in the basal interventricular septum [40]. The afterload-elicited autophagic response continues to increase, peaking at 1 week post-surgery, a time when the most robust growth kinetics are manifested. These observations were corroborated by accumulation of Beclin 1 and lysosomal markers in the myocardium. Consistent, autophagic activity is significantly induced in the angiotensin II-exposed mouse heart [41]. Importantly, a recent paper by Diwan et al. [42] reported that in the context of ischemia/reperfusion injury, autophagosome clearance is impaired by ROS-induced declines in LAMP2 and increases in Beclin1, highlighting context-dependent regulation of this complex pathway. Finally, exposing cardiomyocytes to growth cues *in vitro* triggers significant hypertrophic growth, reactivation

of a fetal gene program and increases in autophagic flux, confirming the myocyte autonomous nature of these events [41, 43, 44].

Metabolic remodeling in cardiac hypertrophy

The metabolic demands of the myocardium are exceptionally high. The never-ending cycles of contraction and relaxation consume large quantities of ATP, which are largely generated from fatty acid oxidation. However, the heart is essentially an omnivore which can flexibly burn fuel derived from a wide range of sources [15].

One of the most dramatic changes occurring with cardiac hypertrophy is a shift in energy substrate utilization, a process termed metabolic remodeling [13, 45]. Numerous studies have shown that upon hypertrophic transformation of the myocardium, glucose uptake and glycolysis are significantly up-regulated while β -oxidation of fatty acid is reduced. Using an isolated heart model, Allard et al. [46] found that glycolysis contributes 19 % of ATP production in the hypertrophic heart compared with 7 % in normal heart. On the other hand, palmitate oxidation accounts for 55 % of total ATP generation in hypertrophic heart compared with 69 % in controls. Likewise, Sorokina et al. [47] reported that flux through β -oxidation is 23 % lower in hypertrophic heart compared to normal heart independent of TCA cycle rate. These results are consistent with the overarching phenomenon of fetal gene program activation in the pathologically stressed myocardium. Lopaschuk et al. [48] found that heart at day 1 post-delivery generates 44 % of its ATP from glycolysis compared with 7 % on day 7. At the same time, they showed that the contribution of cardiac palmitate oxidation increases from 13 % on day 1–39 % on day 7. Collectively, these data indicate hypertrophic heart manifests a dramatic shift in metabolism which mimics the metabolic program in the fetal myocardium.

The metabolic changes characteristic of cardiac hypertrophy have long been appreciated. However, mechanisms underlying these remodeling events remain elusive. Tian and colleagues proposed that the metabolic changes are driven by shifts in substrate availability within the hypertrophied heart; they compared the distributions of metabolites present in hypertrophic versus normal hearts, observing that the concentrations of free ADP, free AMP, free Pi, and fructose-2,6-phosphate were each significantly up-regulated [49]. These molecules are established activators of the rate-limiting enzymes of glycolysis, including PFK1 [50]. Tian and colleagues reported that AMPK, an intracellular energy sensor which is activated by increases in the AMP/ATP ratio, triggers phosphorylation and activation of PFK2 to promote fructose-2,6-phosphate production [49].

Hypoxia has also been implicated in the metabolic alterations occurring with cardiac hypertrophy. During the phase of rapid hypertrophic growth, the relative ratio of myocytes-to-endothelial cells may drop below the ideal range, inducing moderate hypoxia and impacting a cascade of metabolic events. Studying a model of inducible Akt1 overexpression in heart, Walsh and colleagues found that mouse heart manifests a rapid failure phenotype when VEGF signaling is disrupted [51]. Additionally, Krishnan et al. [52] reported that HIF1- α is significantly up-regulated in cardiac hypertrophy induced by pressure overload, strongly stimulating cardiomyocyte glycolytic pathways. Although these findings may explain energetic aspects of hypertrophic cardiac remodeling, they fall short of explaining other important phenomena, including hypertrophic growth, and do not provide convincing evidence to define how the fuel switch and cellular growth coordinate to sustain cardiac function during cardiac hypertrophic remodeling.

Accumulating evidence suggests that the activation of autophagy may play a critical role in both hypertrophic growth and the associated metabolic changes which occur during cardiac remodeling. Hypertrophic growth of cardiomyocytes involves synthesis of new

macromolecules and organelles. To accomplish this, exogenous nutrients, such as glucose, cannot be metabolized exclusively for ATP production. Rather, metabolic intermediates must be channeled to support anabolic pathways. For example, glucose-6-phosphate is a major substrate for glycolysis; it is also critical in the generation of NADPH to provide reducing equivalents required for de novo fatty acid biosynthesis, which may contribute to overall lipid synthesis in heart. Up-regulation of glucose uptake and glucose phosphorylation, each characteristic of hypertrophic cardiac remodeling, may thus support both energy generation and synthesis of new macromolecules. This, combined with the actions of autophagy to provide key intermediate metabolites that feed into the TCA cycle, culminates in interplay of actions that govern the balance between ATP production and macromolecule synthesis.

Enhancement of glucose utilization during cardiac remodeling may inhibit fatty acid β -oxidation. Moreover, augmented demand for lipids to support membrane biosynthesis may further decrease flux into the β -oxidation pathway. These effects, when combined, may lower acetyl-CoA levels within mitochondria and negatively impact the TCA cycle and consequent ATP generation. Additionally, intermediates of the TCA cycle may be selectively extracted to the cytosol for synthetic purposes. For example, citrate can be transported to the cytoplasm, providing cytosolic acetyl-CoA for de novo lipogenesis. Guo and colleagues found that autophagic activity is required in a cancer model to maintain intermediate metabolite levels and to maintain flux through the TCA cycle [53]. It is thus possible that up-regulated autophagy in cardiac hypertrophy functions as an essential means to provide critical molecular intermediates necessary to maintain TCA flux and energy generation (Fig. 2).

Thus, nutrient flux from autophagy may support metabolic remodeling and macromolecular biosynthesis at various levels (Fig. 3) [54]. Nucleic acid degradation may provide nucleotides to synthesize new DNA and RNA. Alternatively, ribose derived from nucleotides can feed into glycolysis via the pentose phosphate pathway. Metabolized sugars can provide substrates for glycolysis or for glycan synthesis. Finally, amino acids are critical to provide several key intermediates of the TCA cycle, such as pyruvate, oxaloacetate, succinate-CoA, and α -ketoglutarate [55].

During hypertrophic growth of any cell, anabolic pathways are significantly up-regulated, and associated augmentation of energy demand promotes mitochondrial biogenesis. Lehman et al. [56] reported that overexpression of PGC1 α in cardiomyocytes promotes expression of energy production genes and increases mitochondrial biomass. Likewise, the biosynthetic regulator, mTOR, is activated during hypertrophic growth. Inhibition of mTOR activity by rapamycin regresses cardiac hypertrophic growth triggered by pressure overload [57]. Interestingly, recent studies indicate that starvation-induced autophagy is required to activate the mTOR pathway and recycle nutrients required for biomass synthesis [58].

Collectively, autophagy in cardiac hypertrophy may contribute significantly to both energy production (via glycolysis and the TCA cycle) and augmented biosynthesis by recycling and replenishing stores of critical nutrients and metabolites.

Autophagy in heart failure

Mechanisms underlying progression from compensatory cardiac hypertrophy to maladaptive heart failure remain poorly characterized. Numerous changes are involved in this transition, including altered calcium handling, fibrosis, inflammation, and cell death [16]. Multiple lines of evidence reveal that autophagy is potently induced in heart failure [59, 60]. Hein et al. [61] reported evidence of tenfold induction of autophagy in cardiac tissue samples harvested from patients with severe heart failure, noting that this mechanism was more prevalent than

necrosis and apoptosis combined. In a mouse model of severe aortic constriction, we found that autophagy is dramatically up-regulated in a time course which correlates with the development of contractile dysfunction and heart failure [40]. Interestingly, we did not find significant increases in apoptosis. Similarly, Shende et al. [62] found that raptor-deficient animals progress rapidly to heart failure when subjected to pressure overload. Autophagy, in this process, was strongly induced due to inactivation of mTOR signaling. Collectively, these results lend support to a model where autophagy, when overactivated, can become maladaptive and contribute to cardiac dysfunction and heart failure.

Metabolic derangement in heart failure

Heart failure is a multifactorial syndrome which derives from a wide range of diseases. Accumulating evidence, however, suggests that metabolic derangement—characterized as metabolic “burn out”—is a conserved mechanism of heart failure [63, 64]. In cardiac hypertrophy, increases in glycolysis compensate for declines in fatty acid β -oxidation and also promote macromolecule biosynthesis. This alteration of reduced fatty acid uptake and β -oxidation may extend to early stages of heart failure. However, when the process progresses to later stages of heart failure, pathological activation of the sympathetic nervous system stimulates lipolysis, provoking increases in circulating fatty acid levels. This, in turn, enhances fatty acid uptake. These changes occur concomitantly with mitochondrial dysfunction, such that utilization of fatty acids is impeded. In other words, the failing myocyte becomes engorged with lipid—taking in more than it can burn—which promotes lipotoxicity. In addition, dysfunctional mitochondria elicit reactive oxygen species, which renders the situation yet more toxic. Finally, increases in fatty acid use negatively affect glucose metabolism and cardiac performance. Indeed, inhibition of fatty acid metabolism by pharmacological means can effectively ameliorate contractile dysfunction and enhance cardiac performance in multiple heart failure models [64, 65].

Autophagy in heart failure metabolism

The “energy crisis” of heart failure stimulates robust activation of autophagy [66]. In advanced heart failure, myocardial ATP levels drop to 30–40 % of control [67, 68], which activates AMPK signaling. Recent studies show that AMPK can directly up-regulate autophagy by phosphorylating ULK1, an upstream kinase involved in autophagy initiation [69]. Moreover, fatty acid oxidation and oxidative phosphorylation inevitably generate ROS. When the detoxifying system is overwhelmed, excessive ROS causes oxidative damage to proteins, lipids, and organelles, which can directly activate autophagy. Likewise, the inability to efficiently pump blood in heart failure can contribute to a hypoxic milieu, which has been implicated as a potent activator of autophagy.

Activation of autophagy in heart failure may exacerbate the metabolic derangements characteristic of the syndrome (Fig. 4). Excessive autophagy may trigger nonspecific degradation of essential metabolic enzymes and mitochondria, contributing to the crisis of energy. Chaanine et al. [60] reported significant mitochondrial autophagy (also termed mitophagy) in pressure overload heart failure. Moreover, treatment with 3-MA (3-methyladenine), an inhibitor of autophagy, can preserve mitochondrial abundance, improve contractile dysfunction, and reverse the maladaptive remodeling of heart failure. One study employing a selective mitochondrial division/mitophagy inhibitor reported that expression of mitophagy markers was decreased, and cardiac performance improved, after treatment [59]. Using mice haploinsufficient for Beclin 1, we found that inhibition of autophagy similarly enhanced cardiac function and reversed pathological remodeling [40]. Excessive autophagy in heart failure may thus lead to pathological declines in mitochondrial number and function, exacerbating already low levels of ATP. This, in turn, may culminate in a

vicious cycle, where energy crisis begets energy crisis, promoting further heart failure progression.

Perspective

Cardiomyocyte autophagy is activated under a wide range of pathological conditions and participates importantly in the associated shifts in metabolism (Fig. 5). Basal autophagy is essential to degrade long-lived proteins and to clear defective organelles, thereby maintaining cellular homeostasis in most tissues and cells. Starvation-activated autophagy is indispensable to replenish substrates for ATP production and sustain normal cellular homeostasis. Pressure stress on the left ventricle, a common clinical scenario, triggers a robust autophagic response which not only accomplishes critical housekeeping functions, but also directly contributes to metabolic remodeling by enhancing ATP production and cellular growth. When pressure stress on the ventricle is persistent, heart failure ensues, which is characterized by excessive autophagy, declines in the number and function of mitochondria, and perturbations in several aspects of cardiomyocyte metabolic flux. Recent studies suggest that therapeutic titration of autophagy reverses pathological remodeling and improves cardiac performance [44]. These studies, then, highlight autophagy as an attractive therapeutic target for heart failure [70]. More work, however, is required to fully define the metabolic profit and loss conferred by autophagy in cardiac hypertrophy and failure; doing so may uncover novel and specific ways of intervening in these disorders.

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Fig. 1.

The autophagy pathway. To induce autophagy, a dynamic and highly regulated process, the serine/threonine kinase complex ATG1/ATG13/ATG17 is activated when the inhibitory effects of TOR are removed. The lipid kinase VPS34 and anchoring component VPS15 stimulate isolation membrane nucleation. Then, two ubiquitin-like conjugation systems, ATG12 and LC3, contribute to the expansion of the autophagosome. After fusion with a single membrane lysosome, the engulfed cytoplasmic materials are degraded by acid hydrolases within the autolysosome, and nutrients are released to the cytosol for recycling.

Fig. 2.

The interplay between glucose metabolism and autophagy in cardiac hypertrophy. During hypertrophic remodeling, glucose uptake and utilization are increased. In parallel, robust activation of autophagy occurs, contributing to metabolic changes in various ways. Nutrients provided by autophagic degradation can produce glucose-6-phosphate for NADPH production and glycolysis as well as key intermediate metabolites for macromolecule biosynthesis and ATP production. Thus, up-regulation of both glucose metabolism and autophagy in cardiac hypertrophy foster synergistic crosstalk to fulfill goals of enhanced ATP production and biosynthesis

Fig. 3.

Multiple ways in which autophagy participates in metabolic remodeling. Autophagy and lysosomal degradation provide essential nutrients which contribute to energy and biomaterial production. Amino acids may be directly used for new protein synthesis or fueled into the TCA cycle after deamination. Nucleotides can be recycled for new nucleic acid synthesis or to participate in the pentose phosphate pathway (PPP). Sugar moieties from protein/lipid degradation can be channeled to new glycan synthesis or to glucose-6-phosphate for glycolysis. Lipids can feed into the β -oxidation pathway for energy purposes or into the biosynthetic pathway for new membrane generation

Fig. 4.

Metabolic functions of autophagy in heart failure. During the progression from adaptive cardiac hypertrophy to decompensated heart failure, autophagy can be induced by accumulation of reactive oxygen species (ROS) and by oxidized and misfolded proteins. Enhancement of autophagic activity, in turn, can target mitochondria selectively (mitophagy) or indiscriminately, thereby negatively impacting ATP production, exacerbating ROS generation, and promoting disease progression

Fig. 5.

Metabolic profit and loss of autophagy in cardiac hypertrophy and failure. Basal autophagic activity is essential to maintain cardiomyocyte energy production and cellular homeostasis. The significant increase in autophagy seen during cardiac hypertrophy may contribute to adaptive metabolic remodeling, which, together with enhancement of glucose utilization, plays critical roles in ATP production and macromolecule biosynthesis required for hypertrophic growth. The deterioration of energy status in end-stage heart failure triggers exuberant autophagy, which may target mitochondria for degradation, further impairing both glucose and fatty acid metabolism.