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Autophagy: A housekeeper in cardiorenal metabolic health and disease☆

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Abstract

Autophagy, literally translated means self-eating, is a primary degradative pathway and plays an important role in the regulation of cellular homeostasis through elimination of aggregated proteins, damaged organelles, and intracellular pathogens. Autophagy has been classified into microautophagy, macroautophagy, and chaperone-mediated autophagy, depending on the choice of the pathway by which the cellular material is delivered to lysosomes. Dysregulation of autophagy may contribute to the development of cardiorenal metabolic syndrome (CRS), including insulin resistance, obesity, hypertension, maladaptive immune modulation, and associated cardiac and renal disease. Clarifying the pathways and mechanisms of autophagy under normal conditions is essential to understanding its dysregulation in the development of CRS. Here, we highlight a recent surge in autophagy research, such as the cellular quality control through the disposal and recycling of cellular components, and summarize our contemporary understanding of molecular mechanisms of autophagy in diverse organ or tissues involved in the pathogenesis of CRS. This article is part of a Special Issue entitled: Autophagy and protein quality control in cardiometabolic diseases.

Keywords

Autophagy; Cardiorenal metabolic syndrome; Insulin resistance; Obesity; Endoplasmic reticulum stress; Reactive oxygen species

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1. Introduction

The term “autophagy” was coined by Christian de Duve based on his discovery of lysosomes, which won him the Nobel Prize in Physiology or Medicine in 1974 [1]. Autophagy is a cellular degradation pathway that maintains cellular homeostasis through the degradation and recycles cytoplasm components constitutively in response to environmental conditions, such as starvation, endoplasmic reticulum (ER) stress and increased reactive oxygen species (ROS) [2]. There are three types of cell death: apoptosis, necrosis and autophagy. Apoptotic cell death, type 1, is programmed cell death and is characterized by condensation of cytoplasm and chromatin, DNA fragmentation, and cell fragmentation into apoptotic bodies, followed by removal and degradation of the dying cells by phagocytosis [3]. Autophagy cell death type 2 programmed cell death is characterized by the accumulation of autophagic vesicles such as autophagosomes and autophagolysosomes. This process is often observed when massive cell elimination is demanded or when phagocytes do not have easy access to the dying cells [4]. One feature that distinguishes apoptosis from autophagic cell death is the source of the lysosomal enzymes used for degradation of dying cells. Apoptotic cells use phagocytic cell lysosomes for this process, whereas cells with autophagic morphology use the dying cells’ endogenous lysosomal machinery in autophagy [5] (Fig. 1).

Autophagy has been classified into three different types, including microautophagy, macroautophagy, and chaperone-mediated autophagy. Autophagy removes damaged intracellular macromolecules and organelles and plays a protective role for cell survival [6]. Therefore, autophagy not only plays a principal role in the supply of nutrients for cell survival but also plays a constitutive role in cellular homeostasis by acting as a cytoplasmic quality control mechanism to eliminate old or unfolded proteins and damaged organelles [7]. One possible mechanism for autophagy cell protection is elimination of damaged mitochondria, which leads to mitochondrial outer membrane permeabilization and consequent apoptosis. Autophagy involves sequestration of proteins and cell organelles in autophagosomes, which direct them to lysosomes. The formation of autophagosomes is dependent on the induction of several genes, including microtubule-associated protein 1 light chain 3 (LC3), beclin-1, and autophagy-related (Atg) genes [8]. While autophagy plays a critical role in the clearance of degenerated proteins and senescent organelles as well as in the maintenance of cellular homeostasis during energy starvation or stress, dysregulated autophagy has been implicated in the pathogenesis of cardiorenal metabolic syndrome (CRS), which consists of a constellation of cardiac, renal and metabolic disorders including insulin resistance, obesity, metabolic dyslipidemia, maladaptive immune responses and evidence of early cardiac and renal disease [9,10]. Here, we summarize the current understanding of the molecular mechanism of autophagy and the role of autophagy in diverse organs or tissues involved in CRS.

2. Molecular mechanisms and regulation of signaling pathways in autophagy

Autophagy is an extremely complex and tightly regulated cellular phenomenon that involves various physiological and pathological processes. Autophagy incorporates signaling through

the mammalian target of rapamycin (mTOR), 5′ adenosine monophosphate-activated protein kinase (AMPK), and silent information regulator (Sirt) pathways. These steps are induction, nucleation, elongation of phagophores, sequestration of cytosolic components through autophagosome formation, transport to the lysosome, degradation, and utilization of degradation products [11].

2.1. The process of autophagy

The autophagy process begins with the generation of cup-shaped structures called phagophores or isolation membranes mediated by the serine/threonine protein kinase UNC51-like kinase 1 (ULK1) signaling. The two ULK1 sites most dephosphorylated in response to starvation are S638 and S758, which are considered to be mTOR sites, whereas, the potential AMPK sites in ULK1 are phosphorylation of S555, T574, S637, S467, S317, and S777 [12]. These structures elongate to form double-membrane-bound vacuoles named autophagosomes, which engulf cytoplasmic material to be degraded [13]. Nutrient deprivation and rapamycin, an mTOR complex 1 (mTORC1) inhibitor, causes dephosphorylation of ULK1 and dissociation of ULK1 from mTOR C1 ULK1 is thus rendered enzymatically active and leads to increased activity of the beclin-1–vps34 (phosphoinositide 3-kinase, PI3K) complex through phosphorylation of ambra1 and beclin-1[14]. In this process, ambra1 induces autophagy by regulating the stability and kinase activity of ULK1 through interaction with TNF receptor associated factor- 6 [14]. Elongation of the autophagosome is mediated by two conjugated systems comprising Atg12–Atg5–Atg16 and LC3–phosphatidylethanolamine (PE). After formation of complete autophagic vesicles, the mature autophagosome becomes fused with a lysosome to create an autolysosome, where sequestered molecules and organelles are degraded [14,15]. Autophagosomes can directly fuse with lysosomes, or they can further receive inputs from the endocytic pathway and form hybrid organelles named amphisomes. Autophagosomes or amphisomes are then trafficked along the microtubules to the microtubule-organizing center where lysosomes are clustered. Auto-phagosomes then fuse with lysosomes to generate autolysosomes [13]. A key protein in the autophagic process and one of the few markers currently available to monitor autophagy is LC3. LC3 is initially synthesized as its unprocessed form – pro-LC3 – which is converted into a proteolytically processed form – LC3-I – and finally modified into the PE-conjugated form — LC3-II. LC3-II is a reliable protein marker for autophagosome formation [16].

2.2. Regulation of signaling pathways in autophagy

2.2.1. mTORC1 signaling pathway—Autophagy is tightly controlled by mTOR-dependent signaling pathway, which phosphorylates and inhibits the ULK1 kinase complex and prevents autophagy induction [17]. mTOR exists as two distinct protein complexes, mTORC1 and mTORC2, which differ in their subunit composition and sensitivity to rapamycin [18]. In this regard, mTORC1 is a rapamycin-sensitive protein kinase complex involved in the mediation of autophagy, whereas mTORC2 modulates cell growth through regulation of the cytoskeleton [18]. Under nutrient-rich conditions, mTOR is mainly activated through a signaling cascade involving activation of class I phosphinositol 3 kinase (PI3K)/protein kinase B (Akt), phosphorylation of tuberous sclerosis complex 2 (TSC2), and activation of the GTP-binding protein Rheb which in turn activates mTOR [19]. During

starvation, the PI3K/protein kinase B (Akt) pathway is switched off therefore mTOR is inactive [13]. In mammals, compromised cellular energy production inhibits mTOR through activation of AMPK [20]. Our study has found that over-nutrition, obesity, and diabetes activate mTOR signaling through inactivation of AMPK, which may inhibit the ULK1 kinase complex, preventing the initiation of autophagy and resulting in CRS [9,10].

2.2.2. AMPK—AMPK monitors the energy condition of cells by sensing the AMP/ATP ratio. It is activated in response to an increase in the intracellular AMP/ATP ratio during exercise, hypoxia, oxidative stress and glucose deprivation [21]. There are several upstream kinases that can activate AMPK by phosphorylating a threonine residue on its catalytic α subunit such as liver kinase B1, calcium/calmodulin kinase and tissue growth factor (TGF)-β-activated kinase-1 [16]. The mechanisms of AMPK that can activate autophagy include activation of AMPK stimulating JNK1 which mediates bcl-2 phosphorylation and subsequent beclin 1–bcl-2 dissociation, controlling the Forkhead box O (FoxO) transcription factors which induce the expression of autophagy-related genes, phosphorylation of ULK1, and directly phosphorylating beclin 1 [22]. Interestingly, AMPK activity is significantly suppressed in diabetic mice, and data suggests that AMPK reduction might be related to a reduction of autophagy and consequent cardiac dysfunction [23]. Indeed, there is a reciprocal relationship between AMPK and mTOR signaling pathways which emphasizes the complex signaling cascades involved in autophagy [24].

2.2.3. Sirtuins—The mammalian genome encodes seven sirtuin (Sirt) isoforms which consist of silent information regulator Sirt1 to Sirt7 [25]. Sirt1, a prototype Sirt isoform, has been the most studied in relationship to autophagy. Recent studies suggest that Sirt1 may be localized in the plasma membrane, where it upregulates insulin metabolic signaling and modulates cell survival, apoptosis, autophagy, and metabolism [25]. Sirt2 is a cytoplasmic deacetylase that deacetylates tubulin and also regulates cytoskeletal reorganization, autophagy, and metabolism [26]. Sirt1 can directly interact with and deacetylate several Atg proteins, including Atg5, Atg7, and Atg8, leading to the activation of these autophagic proteins [27]. Furthermore, Sirt1 deacetylates the transcription factor FoxO3, which leads to enhanced expression of proautophagic bcl-2 interacting protein 3 (Bnip3). In addition, Sirt1 through crosstalk with the AMPK and mTOR pathways can regulate metabolic functions including autophagy [28]. An increase in the intracellular concentration of NAD^+ by caloric restriction can activate Sirt1. However, NAD^+/NADH ratios are decreased in cells under conditions with over-nutrition [18]. Thus, the expression of Sirt1 decreases in obesity, CRS and type 2 diabetes. These data suggest that activation of Sirt1 may have therapeutic efficacy in patients with CRS and diabetes.

3. Autophagic regulators in CRS

Many factors regulate autophagy may play an important role in the pathogenesis of metabolic, cardiac and renal abnormalities that characterize CRS, including nutrient status, ER stress, inflammation, as well as ROS.

3.1. Nutrient status

Autophagy is rapidly activated in response to nutrient and energy stresses, such as inadequate nutrient supply and deprivation of growth factors. Nutrient starvation leads to an elevated AMP/ATP ratio, which activates AMPK and consequently enhances autophagic activity [29]. Activation of the mTORC1 is also independently regulated by intracellular levels of amino acids, especially branched chain amino acids. When the levels of amino acids present in the cell are sufficient, mTORC1 receives signals that promote its activity and suppress autophagy [22]. For example, leucine, a branched chain amino acid can activate mTORC1 and inhibit autophagy through a bidirectional system that coordinates efflux of intracellular glutamine and influx of essential amino acids. In starvation, amino acids released from skeletal muscle or other tissues are utilized as substrates for gluconeogenesis [14]. Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine secreted by various tissues and regulates autophagy under starvation. The mechanism through which MIF exerts its cardioprotective effect is believed to be dependent upon activation of its cardiac receptor CD74, promoting AMPK activity, and inhibiting Jun amino-terminal kinases (JNK)/mitogen-activated protein kinases (MAPK) in response to starvation [30]. Since skeletal muscle represents a large part of the total protein pool in the body, autophagic protein degradation in skeletal muscle may be important in regulation of blood amino acids during fasting [31]. Therefore, autophagic proteolysis plays an important role in the maintenance of an adequate amino acid pool and of energy homeostasis after nutrient deprivation.

Insulin metabolic signaling and glucose metabolism are intimately related to cellular autophagy and associated glycolysis, ER stress, and ROS levels. In conditions of glucose deprivation, autophagy can, on the one hand, use and store glycogen to generate glucose. On the other hand, glucose levels influence glycosylation, glycolysis, and redox status, which have complex relationships with the regulation of autophagy [32]. Diversity of the pathways involved in glucose regulation of autophagy might be attributable to differences in cell types and situation. For example, glucose deprivation in cardiomyocytes, a condition similar to myocardial ischemia, induces autophagy. The induction of autophagy degrades proteins and organelles, generating fatty acids and amino acids for energy production, which prevents cardiac cell death and improves myocardial ischemia tolerance [33]. However, over-nutrition disrupts cardiac autophagosome maturation and suppresses autophagy via activation of PI3K/Akt and mTOR/S6K signaling [34].

Triglycerides are stored in lipid droplets which can be hydrolyzed into glycerol and free fatty acids (FFAs) during times of nutrient starvation. Interestingly, studies have shown that autophagy also participates in the degradation of lipid droplets. In starvation, lipid droplets are engulfed by autophagosomes and transferred to lysosomes in which the lipids are degraded by lysosomal acid lipases [31]. Increased levels of FFAs increase autophagic activity through inhibiting mTORC1, promoting activation of eukaryotic initiation factor 2 (eIF-2α), and enhancing activation of protein kinase C (PKC) [14]. However, dyslipidemia, a major characteristic of CRS, has been reported to impair autophagic processes. A high fat diet (HFD) increases serum levels of triglycerides and cholesterol and leads to impaired autophagy. The impairment of autophagy due to prolonged lipid exposure can be attributed

to defects in autophagosome and lysosome fusion [29]. In this regard, HFD significantly suppresses the expression of Rab7, which is a small GTPase protein capable of stimulating lysosomal biogenesis and autophagic vacuoles maturation by promoting their fusion with endosomes and lysosomes. However, the effect induced by HFD is abolished by Akt2 knockout [35]. Thus, Rab7 is involved in the HFD and Akt2 regulating autophagosome maturation process and inhibition of autophagy may lead to accumulation of intracellular triglycerides and impaired insulin metabolic signaling.

3.2. Endoplasmic reticulum (ER) stress

The ER is an important posttranslational modification site in eukaryotic cells, and is responsible for maintenance of proper protein folding of almost a third of proteins synthesized in the cell [36]. Over-nutrition, inflammation, and increases in ROS can cause cellular damage through protein oxidation, improper protein folding caused by ER stress, DNA damage, and intrinsic action on mitochondria, cell toxicity and several other mechanisms [37]. ER stress results in an adaptive response, termed the unfolded protein response (UPR), which results in increased proteasomal degradation of improperly folded proteins. ER stress is linked to obesity, inflammation and insulin resistance in CRS and type 2 diabetes [37].

The ER is not only involved in protein synthesis and maturation but may also constitute a major autophagic isolation membrane. UPR, a major ER stress pathway, is a potent stimulus of autophagy [16]. Autophagy induced by ER stress plays an important role in maintaining cellular homeostasis through alleviating stress. The ER is related to two major degradation processes in eukaryotic cells that include the ubiquitin–proteasome pathway and the autophagy–lysosome pathway [38]. Autophagy induced by ER stress can also degrade the mis-folded proteins, which exist in the ER lumen and could not be removed by the endoplasmic-reticulum-associated protein degradation (ERAD) pathway [38]. Thus, therapeutic interventions that target molecules of the UPR component or reduce ER stress, such as increasing cellular antioxidants, chaperone capacity, or autophagy levels, may bring the balance toward homeostasis and provide promising strategies for treating ER stress-related human diseases such as CRS and type 2 diabetes.

3.3. ROS, mitophagy, and inflammation

ROS production occurs mainly at complex I and complex III in mitochondria [39]. Under conditions of over-nutrition, nutrient overflow into cells induces an increase in electron transfer to oxygen without ATP production. This, in turn, favors a state of increased ROS, which potentially leads to oxidative damage within mitochondria [40]. Therefore, ROS generated from mitochondria damages proteins, DNA, and lipid membrane components, which results in mitochondrial dysfunction. It has been reported that ROS induces autophagy through multiple mechanisms. Some reports have shown that exogenous hydrogen peroxide can activate PKR-like kinase (PERK), which subsequently phosphorylates eIF2a, oxidizes and activates Atg4 proteases, and thereby accelerates the production of proteolytic mature LC3 and inhibition of mTORC1 activity [16]. ROS also can activate autophagy through JNK. Furthermore, cells must remove damaged mitochondria to prevent the accumulation of ROS [41]. These mechanisms involve selective

sequestration and subsequent degradation of the dysfunctional mitochondrion before it causes activation of cell death. This occurs through an autophagic process in mitochondria also known as mitophagy [42]. Therefore, autophagy can be either a self-protective mechanism mitigating oxidative stress and inflammation or a self-destructing process stimulating mitophagic cell death.

ROS production may induce a chronic inflammatory and an increased inflammatory activation which has also been linked to CRS [43]. The proinflammatory cytokines, such as tumor necrosis factor-α (TNFα), Interleukin 6 (IL6), and c-reactive protein (CRP) are elevated in patients with insulin resistance and type 2 diabetes [44]. Suppression of proinflammatory responses represents a promising strategy to combat obesity and insulin resistance in CRS. However, many of the intracellular signaling cascades in inflammation are affected by activating toll-like receptors (TLRs), which are critical components in the pathology of heart, kidney and liver cell death in CRS. For example, lipopolysaccharide (LPS)-induced autophagy was observed to be markedly inhibited in cells transfected with a vector that overproduces an inactive TLR4, and knockdown of TLR4 using small interfering RNA completely abrogates the induction of autophagy by LPS [45]. These studies provide evidence for a connection among inflammation, TLR signaling and autophagy and hint at the possibility of inducing selective autophagy to protect against FFA-induced cell dysfunction with an adaptive manner in CRS.

4. Impact of autophagy on CRS

Since autophagy plays a key role in the metabolism of lipids, glucose, and recycling of damaged organelles, autophagy dysfunction may contribute to the abnormal characteristics of CRS including obesity, insulin resistance, diabetes, and cardiovascular diseases (Fig. 1).

4.1. Obesity

Adipose tissue, a major current pandemic of obesity and metabolic diseases, may produce over 50 active substances, such as monocyte chemotactic protein-1 (MCP-1), TNF-α, IL-6, CRP, and angiotensin II (Ang II) which when released into the circulation are involved in the regulation of energy balance, lipid metabolism, insulin sensitivity, immune response, angiogenesis, vascular function, arterial blood pressure, coagulation and acute inflammation [46]. The function of autophagy in adipose tissue includes two aspects: firstly, it is required for cytoplasmic reorganization and mitochondrial clearance during adipogenesis; secondly, it is also likely involved in the regulation of mitochondrial homeostasis in mature adipocytes [47]. A recent study has shown an increase in autophagic activity in the adipose tissue of obese subjects. Obesity and caloric overfeeding are associated with the defective regulation of autophagy in the adipose tissue [48]. The degree of fat accumulation and fat cell hypertrophy are the factors that are most strongly associated with autophagy gene expression, and altered autophagy is accentuated in obesity-related insulin resistance in CRS [49] (Fig. 1).

4.2. Insulin resistance and type 2 diabetes

Type 2 diabetes is characterized by dyslipidemia, insulin resistance, and failure of the pancreatic β-cells to produce adequate insulin. One of the proposed causes for the onset of β-cell deterioration in type 2 diabetes is diet-induced nutrient surplus [50]. Autophagy is important in the maintenance of β-cell mass, structure, and function in the insulin-producing pancreatic β-cells under stressful environments [51]. For example, chronic glucose overload and FFAs lead to an unsustainable increase in insulin demand, resulting in toxic ER, oxidative stress, eventually affecting the expression of autophagic genes within β-cells [15]. If autophagy were dysfunctional, as hypothesized in type 2 diabetes, the build-up of misfolded proteins and ER/oxidative stress products caused by hyperglycemia and lipotoxicity would invariably lead to β-cell damage and death. The study further confirmed that the Akt signaling pathway is activated under energy-rich conditions. The activated Akt phosphorylates activate the mTOR kinase resulting in suppression of autophagy in turn [29]. Consistent with this hypothesis, recent data suggests that stimulation of autophagy reduces apoptosis induced by FFAs and increases cell survival of β-cells in CRS [13]. These data suggest that autophagy may be critical to remove these aggregates and protect from ER stress-induced β-cell death under insulin-resistant conditions.

4.3. Cardiac diseases

Diastolic dysfunction is the most common and earliest functional abnormality observed in patients with CRS and diabetes. Although the physiology of diastolic function is complex, the intrinsic left ventricular (LV) abnormalities contributing to LV diastolic dysfunction (LVDD) are impaired LV relaxation, increased LV asynchrony, and hypertrophy [49]. Compared to individuals without diabetes, diabetic patients had higher left ventricle mass and greater wall thickness [52]. Furthermore, LVDD in hypertrophied hearts contributes to heart failure with preserved ejection, consisting of prolonged isovolumic LV relaxation, slow LV filling, and increased LV stiffness [53]. Autophagy has been observed to suggest that cardiac-specific loss of Atg5 is associated with heart failure caused diabetic cardiomyopathy. But the interplay between diabetes and autophagy signaling appears particularly complex [54]. Studies have demonstrated that upregulation of autophagy plays a protective role in the heart. For example, chronic ischemia stimulated autophagy and autophagosomes were seen in surviving cardiomyocytes but not in apoptotic ones in a swine model [29]. Conversely, autophagy may be detrimental during reperfusion through a beclin 1-dependent but AMPK-independent mechanism [55]. Moreover, overexpression of beclin1 in the heart amplified the autophagic response in response to pressure-overload stress, leading to cardiac hypertrophy, cardiac fibrosis, and cardiac dysfunction, suggesting that enhanced autophagic activity by overexpression of beclin1 may have pathological consequences [56]. Thus, maintaining adequate levels of autophagy is important for clearing dysfunctional cell components in the diabetic heart. However, it is important to note that chronic or overactive autophagy can have severely detrimental effects in the heart and contributes to pathogenesis in diabetic cardiomyopathy [22]. It is therefore critical to maintain a balance between autophagy sufficient to regulate the cellular homeostasis and excessive autophagy that can cause cell stress. Clearly, it remains largely unknown what determines the beneficial or detrimental nature of autophagy under each of these cardiac conditions.

4.4. Vascular diseases

The metabolic abnormalities that characterize diabetes, hyperglycemia, FFA, and insulin resistance provoke the impairment of the function and structures in blood vessels, such as endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) [57]. Low-density lipoprotein (LDL) particles invade the endothelium and become oxidized, creating risk for a subsequent inflammatory response and ultimately cardiovascular diseases. Monocytes enter the artery wall from the bloodstream with platelets adhering to the area of insult, differentiate into macrophages, and eventually form foam cells. Foam cells die and further propagate the atherosclerotic process [58]. Interestingly, both VSMCs and macrophage autophagy are known to be critical during the process of vascular diseases [59]. A study has found that atheromas showed strong fluorescence background which could interfere with imaging of fluorescently labeled LC3 [60] and further confirmed that autophagy was activated by several mechanisms including oxidized LDL, ER stress, inflammation cytokines, hypoxia, and metabolic stress [54]. It has been reported that inhibiting autophagy in macrophages by silencing Atg5 led to both increased apoptosis and plaque instability in advanced lesions, which increased the risk of plaque rupture [61]. It is possible that attenuation of autophagy in these macrophages led to the accumulation of damaged materials such as misfolded proteins and damaged mitochondria that triggered apoptosis. Such a finding indicates a beneficial role of autophagy in vascular diseases. However, overactive autophagy has also harmful roles in vascular diseases since overactive autophagy may eventually trigger autophagy-induced cell death resulting in plaque destabilization and is considered a crucial step in the development of myocardial infarction and stroke [61]. Thus, we should clearly know if the roles of autophagy could be either protective or detrimental in vascular diseases.

4.5. Autophagy and renin angiotensin aldosterone system

There is evidence that renin angiotensin aldosterone system (RAAS) activation plays an important role in the regulation of autophagy in CRS. Our study has also found that Ang II increased serine phosphorylation of Insulin receptor substrate 1/2 and inhibited the insulin-stimulated phosphorylation of endothelial nitric oxide synthase through activation of mTOR signaling pathway [9]. A study has demonstrated that Ang II increased autophagosome formation via the Ang II receptor type 1 receptor 1 (AT-1R) and this response was constitutively antagonized by co-expression of AT-2R in neonatal cardiomyocytes [62]. Thus, autophagic activity increases in the heart in response to a variety of stresses including RAAS. Meanwhile, elevated levels of aldosterone or Ang II increased the abundance of certain proteins such as ribosomal protein L27 and keratin 5, and heat shock protein cognate 70-4, which are indicative of an elevated risk of protein aggregation [63]. Furthermore, Ang II induced the autophagy in mouse podocytes from the kidney through increasing ROS generation [64]. Therefore, there is a link between RAAS and autophagy regulation in the CRS.

5. Conclusion

Autophagy is an important process necessary for maintaining cellular homeostasis and quality control of organelles such as ER and mitochondria. However, dysregulated

autophagy may play a role in the pathogenesis of a constellation of cardiac, renal and metabolic disorders including insulin resistance, obesity, metabolic dyslipidemia, and cardiovascular disease. The regulation of autophagy is complex, and the role of dysfunctional autophagy involved in the balance between cell survival and death in CRS has only recently been established. Therefore, it is hard to predict whether modulation of autophagic activity alone will appreciably improve metabolic profiles since CRS such as obesity and multiple metabolic factors involved in CRS and diabetes. Additional studies are necessary in order to develop safe and clinically effective autophagy modulators that target metabolic and cardiovascular abnormalities in CRS.

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Abbreviations

CRS	cardiorenal metabolic syndrome
ER	endoplasmic reticulum
ROS	reactive oxygen species
LC3	microtubule-associated protein 1 light chain 3
Atg	autophagy-related gene
mTOR	mammalian target of rapamycin
AMPK	5′ adenosine monophosphate-activated protein kinase
Sirt	silent information regulator
ULK1	UNC51-like kinase 1
PI3K	phosphoinositide 3-kinase
FoxO	Forkhead box O
Bnip3	bcl-2 interacting protein 3
FFAs	fatty acids
HFD	high fat diet
UPR	unfolded protein response
eIF-2α	eukaryotic initiation factor 2
LV	left ventricular
LVDD	LV diastolic dysfunction
ECs	endothelial cells
VSMCs	vascular smooth muscle cells
LDL	low-density lipoprotein

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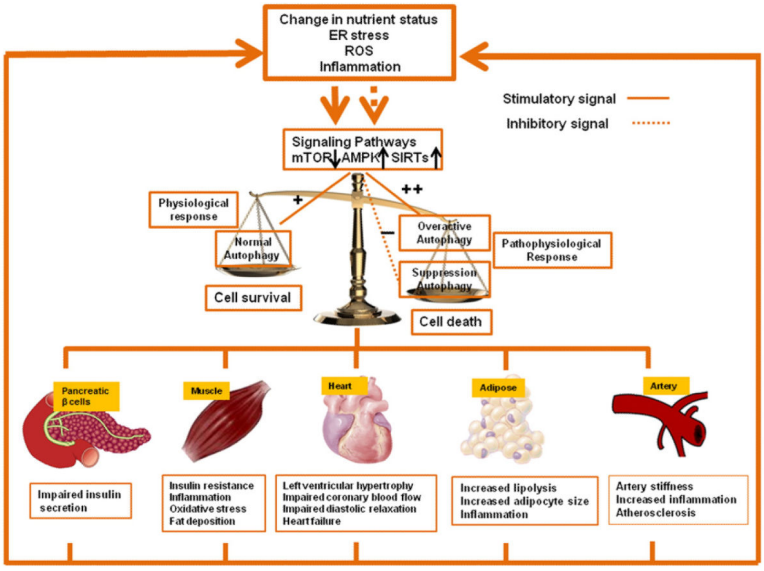

Fig. 1.

Proposed dysregulation of autophagy in the development of CRS. Autophagy is an extremely complex and tightly regulated cellular process in various human physiological and pathological processes. Many factors such as nutrient status, ER stress, inflammation, as well as ROS regulate the autophagy through mTOR, AMPK, and Sirts signaling pathways and eventually cause dysfunction of heart, vascular, adipose, skeletal muscle, and pancreatic β-cells in CRS. These pathophysiological changes furthermore bring out the risk factors in the dysregulation of autophagy in a potentially vicious cycle manner.