Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Minireview

Role of autophagy in metabolic syndrome-associated heart disease ☆

Sidney Y. Ren, Xihui Xu *

Center for Cardiovascular Research and Alternative Medicine, School of Pharmacy, University of Wyoming College of Health Sciences, Laramie, WY 82071, USA

ARTICLE INFO

Article history:
Received 14 February 2014
Received in revised form 21 April 2014
Accepted 29 April 2014
Available online xxxx

Keywords:
Autophagy
Heart
Metabolic syndrome
High fat diet
Obesity

ABSTRACT

Metabolic syndrome (MetS) is a constellation of multiple metabolic risk factors including abdominal obesity, glucose intolerance, insulin resistance, dyslipidemia and hypertension. Over the past decades, the prevalence of metabolic syndrome has increased dramatically, imposing a devastating, pandemic health threat. More importantly, individuals with metabolic syndrome are at an increased risk of diabetes mellitus and overall cardiovascular diseases. One of the common comorbidities of metabolic syndrome is heart anomalies leading to the loss of cardiomyocytes, cardiac dysfunction and ultimately heart failure. Up-to-date, a plethora of cell signaling pathways have been postulated for the pathogenesis of cardiac complications in obesity including lipotoxicity, inflammation, oxidative stress, apoptosis and sympathetic overactivation although the precise mechanism of action underscoring obesity-associated heart dysfunction remains elusive. Recent evidence has indicated a potential role of protein quality control in components of metabolic syndrome. Within the protein quality control system, the autophagy–lysosome pathway is an evolutionarily conserved pathway responsible for bulk degradation of large intracellular organelles and protein aggregates. Autophagy has been demonstrated to play an indispensible role in the maintenance of cardiac geometry and function under both physiological and pathological conditions. Accumulating studies have demonstrated that autophagy plays a pivotal role in the etiology of cardiac anomalies under obesity and metabolic syndrome. In this minireview, we will discuss on how autophagy is involved in the regulation of cardiac function in obesity and metabolic syndrome. This article is part of a Special Issue entitled: Autophagy and protein quality control in cardiometabolic diseases.

1. Introduction

Metabolic syndrome (MetS), previously termed as *Syndrome X*, was originally defined as a constellation of devastating metabolic disturbances, including hyperglycemia, dyslipidemia and hypertension. Subsequent experimental, clinical and epidemiological studies demonstrated that abdominal obesity is also closely associated with the etiology of metabolic syndrome [1]. Although a number of health organizations including the World Health Organization (WHO), the National Health and Nutrition Examination (NHANES), the European Group for the Study of Insulin Resistance and the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATPIII), have somewhat disparate definitions for metabolic syndrome, the essential core components for metabolic syndrome are reminiscent namely central obesity, glucose intolerance, insulin resistance, dyslipidemia and hypertension [2–5].

Over the last decades, the rate of metabolic syndrome-caused death rose dramatically in the United States and other parts of the world. Data from the NHANES III Survey (1998–1994) suggested that the unadjusted prevalence and age-adjusted prevalence of metabolic syndrome as defined by ATP (Adult Treatment Panel) III were 21.8% and 23.7%, respectively, in the United States [6]. In the following 5 years, a significant increase was observed in the prevalence of metabolic syndrome in the United States. According to the report from NHANES 1999–2000, the unadjusted prevalence and age-adjusted prevalence of metabolic syndrome were increased to 26.7% and 27%, respectively [7]. Interestingly, the prevalence of metabolic syndrome is found to be highly age-dependent. Based on the data from NHANES III survey, the prevalence of metabolic syndrome was only 6.7% among participants aged 20–29 years. However, more than 40% of participants aged 60 or above were found to be afflicted with metabolic syndrome [6]. The total population of adults suffering from metabolic syndrome increased dramatically from ~41 million in 1990 to 55 million in 2000 [7]. Considering that obesity (one of the core components of metabolic syndrome) is rapidly approaching an epidemic proportion in the United States, there is an alarming high prevalence of metabolic syndrome in Americans. The prevalence of being overweight or obese among US adults is around 68.2% in 2010, affecting 154.7 million of the US adults [8]. In particular, there has been a dramatic increase in overweight children and adolescents. For example, in the NHANES from 1999 to 2002, 31% of children and adolescents aged 6 to 19 years were at risk of being overweight or obese. This trend continues to rise resulting in 16.9% of US children being afflicted with obesity in 2010 [8]. Not surprisingly, the prevalence of metabolic syndrome was significantly higher in severely obese young individuals [body mass index

☆ This article is part of a Special Issue entitled: Autophagy and protein quality control in cardiometabolic diseases.

* Corresponding author. Tel.: +1 307 766 6133; fax: +1 307 766 2953.
E-mail address: xxu6@uwyo.edu (X. Xu).

http://dx.doi.org/10.1016/j.bbadis.2014.04.029
0925-4439/

(BMI) > 35] [9,10]. Because metabolic syndrome is a combination of metabolic disturbances (all of which are well documented candidates for cardiovascular diseases) it is not unexpected that it can induce cardiac injury and dysfunction [11,12]. Although it is extensively studied, the mechanisms underlying the development of cardiac injury under metabolic syndrome still remain elusive [5,13].

Autophagy (from the Greek auto, meaning 'self', and phagy, meaning 'to eat') is an evolutionarily conserved pathway for bulk degradation of large intracellular organelles and protein aggregates [14]. It is a highly dynamic process, characterized by the formation of a double-membrane vacuole (autophagosome). After fusing with lysosomes, the inner membrane and the engulfed components of the autophagosome are degraded by lysosome, forming a single-membrane vacuole structure called autophagolysosome/autolysosome [13]. It is widely accepted that basal autophagy possesses an indispensible role in the maintenance of cardiac geometry and function under physiological conditions [15–17]. However, cardiac autophagy is susceptible to various cardiovascular insults such as ischemia–reperfusion injury [18], pressure overload [19], and certain cardiotoxic drugs including doxorubicin [20]. Interestingly, accumulating evidence suggests that disturbed autophagy is involved in the onset and development of cardiac injuries in metabolic syndrome [11,12,21,22]. However, disparate results have been noted for autophagy in the heart depending upon the state of metabolic syndrome [11,12,21,22]. For example, one study reported that cardiac autophagy initiation was suppressed in atherogenic diet-induced obesity, insulin resistance and dyslipidemia [11]; another two studies showed that myocardial autophagy was unaffected in high fat diet-induced obesity, insulin resistance and dyslipidemia [21,22]; our studies indicated that myocardial autophagosome maturation was disrupted in high fat diet-induced obesity, glucose resistance, insulin resistance and dyslipidemia [12].

2. Metabolic syndrome and cardiac anomalies

Since metabolic syndrome is a concurrence of independent risk factors for cardiovascular disease, it is not surprising that individuals with metabolic syndrome are found to be more susceptible for heart injury and contractile dysfunction [23,24]. According to the data from the Botnia clinical study involving Finnish and Swedish participants, the presence of metabolic syndrome dramatically increased morbidity and mortality of cardiovascular disease in these participants [25]. At the same time, a tight association of metabolic syndrome with cardiovascular and the overall mortality was unveiled by an independent clinical study involving middle-aged Finnish men [23]. More importantly, their results demonstrated that cardiovascular disease and all-cause mortality are significantly increased in middle-aged men suffering from metabolic syndrome, even without any baseline cardiovascular diseases [23]. The propensity of cardiovascular disease in metabolic syndrome was also extensively studied in an American population in the San Antonio Heart Study (SAHS) [26]. Based on data obtained from SAHS, 156 out of 2570 participants with metabolic syndrome experienced a cardiovascular event within a time frame of 7.5 years. The overall sensitivity or propensity for predicting cardiovascular disease in metabolic syndrome was 67% [26]. More importantly, accumulating studies have shown that metabolic syndrome is tightly associated with the development of abnormal left ventricular geometry and function [27,28]. Using echocardiography, Japanese descendants with metabolic syndrome displayed left ventricular diastolic dysfunction independent of left ventricular mass and systolic function [29]. Along the same line, compromised left ventricular systolic and diastolic functions were observed in Chinese patients with metabolic syndrome as determined by strain and strain rate imaging [30]. More interestingly, recent studies suggest that metabolic syndrome-associated abnormal left ventricular structure and function are independent of levels of blood pressure and fasting plasma glucose [31], although it is closely tied with epicardial adiposity [27].

In line with the clinical observations in patients with metabolic syndrome, results from experimental models of metabolic syndrome also confirmed unfavorable changes in cardiac geometry and function in metabolic syndrome [11,12,32,33]. Among the various experimental models, diet-induced obesity and metabolic syndrome are deemed a widely accepted model to evaluate metabolic syndrome-associated cardiac anomalies [11,12]. For example, prolonged (5-month) intake of 45% high fat diet induced metabolic syndrome in a mouse model, as evidenced by obesity, glucose intolerance, insulin resistance and dyslipidemia [12,32,33]. In particular, high fat diet-induced metabolic syndrome dramatically altered cardiac geometry and function, as evidenced by decreased fractional shortening and increased ventricular wall thickness, and left ventricular end diastolic and systolic diameters (LVEDD, LVESD) [12,32,33]. Meanwhile, cardiomyocyte contractile function is also remarkably impaired in murine models of high fat diet-induced metabolic syndrome, as evidenced by decreased peak shortening and maximal velocity, and increased time-to-90% relengthening [12,32,33]. These changes in cardiac geometry and function are accompanied with overt interstitial fibrosis and ultrastructural changes following chronic high fat diet feeding [12,33]. In a metabolic syndrome-prone Ossabaw swine model, atherogenic diet was employed to induce metabolic syndrome [11]. Ossabaw pigs developed metabolic syndrome following a 14-week atherogenic diet intake. Although cardiac output and myocardial perfusion increased in these Ossabaw pigs with metabolic syndrome, they displayed myocardial hypoxia associated with increased inflammation, oxidative stress, mitochondrial dysfunction as well as fibrosis [11].

3. Protein quality from autophagy

In eukaryotic cells, there are two major proteolytic systems mediating protein degradation and recycling namely the ubiquitin–proteasome and the autophagy–lysosome pathways. Unlike the ubiquitin–proteasome pathway, the autophagy–lysosome pathway is governing bulk degradation of large cytoplasmic organelles and protein aggregates that cannot be degraded by the proteasome system [34]. As an evolutionarily conserved pathway, autophagy pathway is a highly dynamic process with a step-wise process [12,13]. The hallmark of autophagy is the formation of autophagosome, a double-membrane vacuole in which subcellular cargos are sequestered for degradation [12,13]. After being fused with lysosome, the inner membrane of autophagosome is degraded from a single membrane structure named as autophagolysosome/autolysosome. Within the autophagolysosome, the engulfed proteins and cytoplasmic organelles are degraded by enzymes in the lysosome. Subsequently, free amino acids and fatty acids are generated and released from autophagolysosomes to facilitate cell survival under various stresses, such as starvation [35].

According to the mode of cargo delivery to the lysosome and the selectivity of the system, three different forms of autophagy have been defined: (i) chaperone-mediated autophagy (CMA); (ii) microautophagy; and (iii) macroautophagy [13]. CMA is a lysosomal pathway of proteolysis that is mediated by certain molecular chaperones in the cytosol and in the lysosomal lumen [36]. Both microautophagy and macroautophagy sequestrate and degrade large structures in either a selective or non-selective manner. Macroautophagy, hereafter referred to as autophagy, is the one that is extensively studied and the best understood [12,19,20,35]. According to the selectivity of the target cargo for degradation, autophagy can be further specified into mitophagy (mitochondria), ribophagy (ribosomes), pexophagy (peroxisomes), lipophagy (lipids), and reticulopathy (endoplasmic reticulum) to denote specific target for autophagy [19,37].

3.1. Regulation of autophagy

The autophagy pathway is tightly regulated by various molecules, especially the Atg (AuTophaGy-related gene) family and mammalian target of rapamycin (mTOR) kinase. The Atg family members were first discovered in yeast and many of them have orthologues in

Please cite this article as: S.Y. Ren, X. Xu, Role of autophagy in metabolic syndrome-associated heart disease, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2014.04.029

eukaryotic cells [38]. To date, there are more than 30 Atg gene products identified with an essential regulatory role in autophagy. The proteins encoded by these genes are involved in the regulation of the entire autophagy process, from the nucleation of autophagic vacuoles to the formation of the autophagosomes and autophagolysosomes [38].

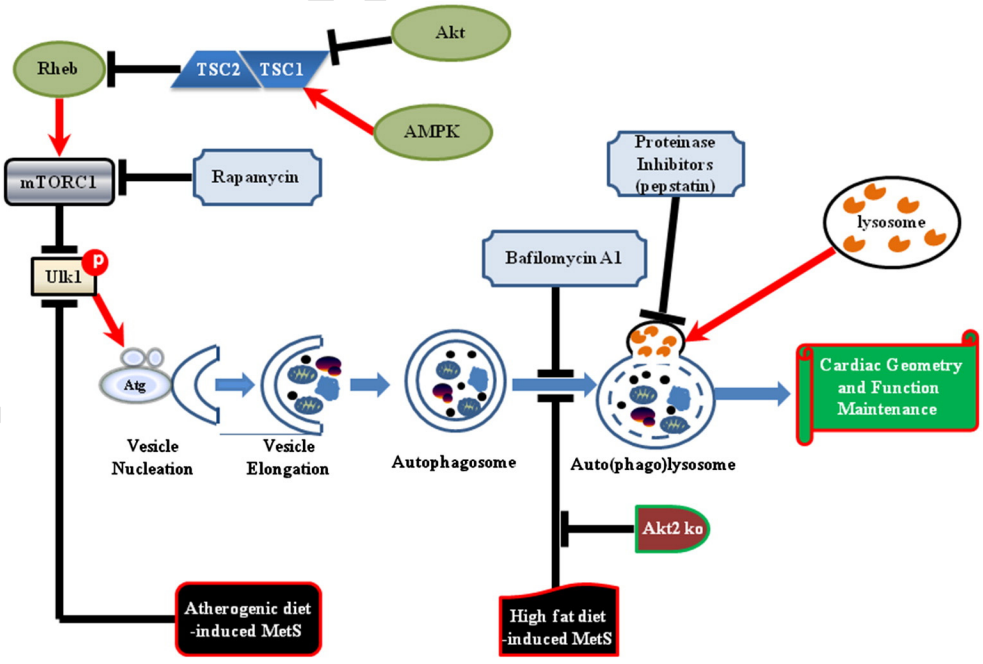
In addition to these Atg proteins, another pivotal player in the regulation of autophagy pathway is mTOR, a kinase regulating protein synthesis and cell growth in response to growth factors, nutrients, energy levels, and stress [39]. Accumulating studies have suggested that mTOR plays an important role in the negative regulation of autophagy [14]. According to the proteins bonded, mTOR complex is divided into two forms, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [40]. mTOC1, consisting of mTOR, raptor and mLST8, is rapamycin-sensitive. mTOC2, containing mTOR, rictor, mLST8, PRAS40, and DEPTOR, is rapamycin-insensitive [40]. Through phosphorylating Ulk1 (the ortholog of mammalian Atg1), mTOR forms a complex with phosphorylated Ulk1, Atg13 and FIP200, thus inhibiting autophagy [40]. Through inhibition of mTOC1, rapamycin is widely employed to induce autophagy [41,42].

On the other hand, mTOR is tightly regulated by its upstream regulator, Ras homology enriched in brain (Rheb). It is believed that Rheb physically binds with mTOR, leading to its activation [43]. At the same time, Rheb is negatively regulated by tuberous sclerosis complex (TSC). TSC is composed of tuberous sclerosis complex 1 (TSC1) and tuberous sclerosis complex 2 (TSC2), where TSC1 is the regulatory component and TSC2 is the catalytic component [43]. Two well-established regulators were present upstream of TSC namely Akt and AMPK. The activity of TSC2 is inhibited by PI3K–Akt primarily through phosphorylation and membrane partitioning [43,44]. In contrast to Akt, AMPK can activate autophagy indirectly by regulating the activity of mTOR. Activated AMPK phosphorylates and activates TSC2, leading to Rheb inhibition and mTORC1 suppression (Scheme 1) [43].

3.2. Regulation of autophagic flux

Since autophagy is a highly dynamic and step-wise process, evaluation of its status based merely on level of Atg members might not be reliable [14]. Traditional methods to evaluate autophagy status include measuring the expression of Atg proteins including Beclin1, LC3B II or the ratio LC3B II/LC3B I, or using microscopy to monitor the number of autophagosomes. However, an increase in the number of autophagosomes does not necessarily reflect the activation of autophagy [12,20,45]. On the one hand, the increase of autophagosomes might indicate that the autophagy is activated [35,42]. On the other hand, it could be the result of decreased degradation by lysosomes [12,20,46]. Therefore, the concept of 'autophagic flux' is introduced to better reflect the dynamic process of autophagy (Scheme 1) [47].

To better evaluate the status of autophagic flux, several assays have now been developed. One of the two commonly employed techniques for the evaluation of autophagic flux in vivo is to assess the number of autophagosomes and the accumulation of its selective substrates. The best studied specific substrate for autophagic degradation is p62/sequestosome 1 (SQSTM) [41]. Since LC3B II is an autophagy marker on the membrane of autophagolysosomes and p62 is selectively degraded by autophagolysosomes, total levels of p62 are inversely correlated with the 'authentic' autophagic activity. Therefore, an increase of LC3B II in combination with a decrease in p62 indicates autophagic flux activation, while an accumulation of both LC3B II and p62 denotes interruption of autophagic flux [12,20,45]. Another widely adopted method to discern autophagy induction from suppressed autophagosome degradation in vivo is to manually inhibit the fusion between autophagosomes with lysosomes or lysosome enzyme activity [14]. Inhibiting the degradation of autophagosomes induces the accumulation of autophagosomes that should be degraded by lysosomes [14]. Accordingly, the difference between the amount of LC3B II detected in the presence or absence of lysosomal inhibitors reflects the amount of LC3B II degraded by autophagolysosomes [14,20,45]. The LC3B II turnover assay has been used to evaluate changes in autophagic flux in murine hearts in vitro and in vivo [20,45]. In in vitro studies, the formation of autophagosomes and autophagolysosomes can be monitored by fluorescence microscopy [45]. This is based on the difference in pH value between autophagosomes and autophagolysosomes. The pH is lower in autophagolysosomes than in autophagosomes, which, in turn, can quench the fluorescent signal of green fluorescent protein (GFP) but not red fluorescent protein (RFP) [45]. Following transfection with monomeric (m)



Scheme 1. Schematic diagram depicting the sequential cellular and molecular aspects of autophagy and autophagic flux affected in the heart under metabolic syndrome (MetS). Autophagy is a highly dynamic process that occurs in a step-wise manner. Red arrows and black lines represent activation and inhibition, respectively. AMPK, AMP-activated protein kinase; Akt: also known as Protein Kinase B (PKB); MetS, Metabolic Syndrome; mTOR, mammalian target of rapamycin; Rheb, Ras homology enriched in brain; TSC, tuberous sclerosis complex; Ulk1, uncoordinated 51-like kinase 1.

Please cite this article as: S.Y. Ren, X. Xu, Role of autophagy in metabolic syndrome-associated heart disease, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2014.04.029

RFP–GFP–LC3, autophagosomes and autophagolysosomes are labeled with yellow fluorescence and red fluorescence, respectively. By assessing the number of yellow and red dots, the formation of autophagosomes and autophagolysosomes can be distinguished for the assessment of autophagic flux [45].

3.3. Autophagy and metabolic syndrome-associated cardiac anomalies

The pivotal role of autophagy in the maintenance of cardiac structure and function has been extensively studied over the past years. It is widely conceived that basal levels of autophagy in physiological conditions are indispensable for cell survival [16]. However, it still remains controversial with regard to the precise role of autophagy in the maintenance of cardiac homeostasis under pathological conditions, especially cardiac hypertrophy and heart failure [19,20,48,49]. Although the correlation between metabolic syndrome and cardiac injury has been extensively documented [5,25,29–31], the role of autophagy in metabolic syndrome-induced cardiac anomalies has not been fully appreciated until recently [11,12,21,22]. To add to the complexity, the current available data of cardiac autophagy in metabolic syndrome appears to be rather conflicting with unchanged [21,22] and decreased autophagy [11], as well as disrupted autophagic flux [12].

The first study describing cardiac autophagy in metabolic syndrome was evaluated in an atherogenic diet-induced Ossabaw swine metabolic syndrome model [11] (Table 1). Metabolic syndrome-prone Ossabaw pigs were fed an atherogenic diet 10 weeks to induce obesity and 14 weeks to induce metabolic syndrome (obesity, dyslipidemia, and insulin resistance). Ten-week atherogenic diet feeding induced ventricular dysfunction with preserved cardiac output. In contrast, 14-week feeding increased cardiac output but lowered myocardial perfusion. Their data on myocardial autophagy in obesity and metabolic syndrome are conflicting. In the state of obesity, the protein level of cardiac Atg5 was significantly increased, while other autophagy markers did not show any significant changes. However, in the state of metabolic syndrome, myocardium displayed increased protein levels of Atg5 but decreased ULK1, Beclin1 and the LC3B II/I ratio (Scheme 1). Although the authors claimed that myocardial autophagy was suppressed in the swine model of metabolic syndrome, their data were in conflict with their statement, especially with the increased expression of Atg5 protein. Furthermore, the autophagic flux was not evaluated in this study. The decrease of autophagy markers, including LC3B II and Beclin1, does not necessarily support the notion of autophagy suppression. It might be explained as the result of autophagy induction [14]. Further studies are required to differentiate autophagy suppression from induction in this Ossabaw swine model of metabolic syndrome. At the same time, metabolic syndrome-induced cardiac anomalies and myocardial autophagy change were examined in a mouse model [22] (Table 1). After 12 weeks of 60% high fat diet feeding, the seventeen-week-old female mice developed metabolic syndrome, as evidenced by obesity, hyperglycemia, hyperinsulinemia and dyslipidemia. In these female mice with metabolic syndrome, cardiac function was suppressed. However, autophagy was unaffected in these mice with metabolic syndrome, as evidenced by the ratio of LC3B II/I and mRNA expression of Atg5. Interestingly, treatment with a carbon monoxide-releasing molecule (CORM-3) increased myocardial autophagy and attenuated cardiac dysfunction without affecting metabolic syndrome. Furthermore, the cardioprotective effect of CORM-3 was dependent on autophagy activation as autophagy inhibition by 3-methyladenine nullified the beneficial effect of CORM-3 [22]. The effect of metabolic syndrome on myocardial autophagy was also reported by a follow-up study [21] (Table 1). Here, 6-week-old male C57 mice were fed 58% high fat diet for ten weeks to induce metabolic syndrome, including obesity, insulin resistance and dyslipidemia. Caloric restriction was found to improve high fat diet-induced metabolic syndrome, the effects of which were associated with myocardial autophagy enhancement [21].

To better understand the cardiac autophagy in metabolic syndrome and associated cardiac injury, a high fat diet-induced murine model of metabolic syndrome and obesity was employed in the laboratory setting [12] (Table 1). Mice were fed a 45% high fat diet for 20 weeks to induce metabolic syndrome, as evidenced by obesity, glucose intolerance, dyslipidemia, and insulin resistance. These high fat fed mice displayed reduced cardiac output and fractional shortening along with compromised cardiomyocyte contractile function and intracellular Ca^{2+} handling. Interestingly, our data suggested possibly activated cardiac autophagy in mice with metabolic syndrome, as evidenced by increased levels of both LC3B I and LC3B II. To further discern contribution of autophagy induction versus suppressed autophagosome degradation to elevated autophagy protein markers, cardiac p62, the specific degradation target by autophagolysosome, was evaluated. Our results showed that p62 protein was significantly increased in the

Table 1
Evaluation for the role of myocardial autophagy under metabolic stress.

Changes in cardiac autophagy	Metabolic disorder model	Authors	Effect in the heart
Activated mTOR; inhibited autophagy	60% high fat diet-induced obesity in mice with glucose intolerance	Sciarretta et al. [52]	Obesity exacerbates cardiac ischemia injury, prevented by mTORC1 inhibition
Inhibited autophagy		He et al. [51]	Bcl2 AAA prevents exercise-induced autophagy activation and protection against high fat diet-induced metabolic changes
Inhibited AMPK, activated; decreased LC3B II/I with unchanged Beclin1	45% high fat diet-induced obesity in mice with glucose intolerance	Guo et al. [50]	Rapamycin negates high fat diet-induced obesity, cardiac anomalies and myocardial suppressed autophagy
Inhibited AMPK, activated Akt–mTOR, disrupted autophagic flux	45% high fat diet-induced metabolic syndrome in mice (obesity, glucose intolerance, insulin resistance)	Xu et al. [12]	Akt2 knockout prevents high fat diet-induced obesity, cardiac injuries and myocardial autophagic flux disruption
Increased Atg5, decreased Ulk1, Beclin1, and LC3B II/I	Atherogenic diet-induced metabolic syndrome in Ossabaw pigs (obesity, insulin resistance, dyslipidemia)	Li et al. [11]	Ossabaw pigs with metabolic syndrome have higher cardiac output but lower myocardial perfusion.
Unchanged AMPK, decreased LC3B II/I	58% high fat diet induced metabolic syndrome (obesity insulin resistance, dyslipidemia)	Cui et al. [21]	Caloric restriction recovers myocardial LC3B II/I without affecting AMPK
Unchanged LC3B II/I and Atg5	60% high fat diet-induced metabolic syndrome in female mice (obesity, insulin resistance, glucose intolerance)	Lancel et al. [22]	Carbon monoxide-releasing molecule increases autophagy marker expression, protects high fat diet-induced mitochondrial dysfunction, nullified by 3-methyladenine.
Increased myocardial LC3B II/I	60% high fructose diet-induced insulin resistance	Mellor et al. [55]	Fructose increases cardiac superoxide production and interstitial fibrosis, suppresses cell survival signaling
Decreased AMPK and LC3B II/I	Diabetic OVE26 mice	Xie et al. [53]	Metformin rescues myocardial AMPK, autophagy, and cardiac functions
Inhibited autophagic flux	STZ-induced type 1 diabetes mellitus	Xu et al. [54]	Beclin1 and Atg16 deficiency protect while Beclin1 overexpression exacerbates STZ-induced cardiac injury.

Please cite this article as: S.Y. Ren, X. Xu, Role of autophagy in metabolic syndrome-associated heart disease, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2014.04.029

heart from mice with metabolic syndrome. These data suggest the presence of activated autophagy initiation along with inhibited autophagosome degradation in hearts from mice with metabolic syndrome. To further confirm that cardiac autophagosome degradation is suppressed in high fat diet-induced metabolic syndrome model, transmission electron microscopy (TEM) was employed for the assessment of autophagosomes and autophagolysosomes. We observed that the number of double-membrane vacuoles, characteristic of autophagosome, was much higher in cardiac tissues in mice following high fat diet feeding. However, the number of single-membrane vacuoles, representing autophagolysosomes, was not significantly increased by high fat diet feeding. The accumulation of double-membrane but not single-membrane vacuoles indicates that high fat diet-induced metabolic syndrome stimulates autophagy initiation but not accompanied rise in autophagosome degradation. Our further analysis revealed that high fat diet feeding-induced inhibition of autophagosome degradation was probably mediated through downregulation of Rab7, a small GTPase responsible for fusion between autophagosome and lysosome [45]. More interestingly, our data revealed that Akt2 knockout effectively rescued cardiac geometric and functional anomalies, probably through reversing the suppressed autophagosome degradation in high fat diet-induced metabolic syndrome (Scheme 1) [12]. However, it is still elusive with regard to how Akt2 regulates Rab7 and autophagic flux in the heart from mice with metabolic syndrome.

The discrepancies with regard to the effect of metabolic syndrome on myocardial autophagy may be attributed to fundamental differences in experimental models [11,12,21,22]. For example, atherogenic diet was used to induce metabolic syndrome in the Ossabaw swine [11], while a mouse model of the metabolic syndrome was induced by chronic high fat diet feeding [12,21,22]. In murine models of metabolic syndrome, the different findings about myocardial autophagy may be attributed to differences in diet composition, time course of diet feeding, animal gender and age [12,21,22]. In the studies in which myocardial autophagy was unaffected by metabolic syndrome, five-week-old female C57BL/6 mice were fed 60% high fat diet for 12 weeks by Lancel et al. [22], and Cui et al. gave 6-week-old male C57 mice male mice 58% high fat diet for 10 weeks [21]. In contrast, 12-week-old male C57BL/6 mice were fed 45% high fat diet for 20 weeks in our model of metabolic syndrome [12].

The effect of obesity, insulin resistance, and diabetes on cardiac autophagy has been carefully evaluated by several independent studies [50–54] (Table 1). He et al. evaluated cardiac autophagy in a mouse model of obesity induced by 60% high fat diet feeding for 12 weeks [51]. Their data revealed that the protein level of p62 was dramatically increased in the heart tissue, without significant changes in the ratio of LC3B-II/LC3B-I in high fat diet-induced obese mice. In another study, mice were fed high fat diet containing 60% fat for 18 to 20 weeks before the heart was harvested for autophagy activity analysis [45]. These obese mice displayed cardiac hypertrophy with preserved fractional shortening. Interestingly, their data showed that cardiac autophagy was significantly suppressed in high fat diet-induced obesity, as evidenced by decreased LC3B II and increased p62 accumulation [45]. In addition, myocardial autophagy suppression was reported in another mouse model of obesity induced by 45% high fat diet feeding [50]. In a mouse model of insulin resistance, male C57 mice were fed a high fructose (60%) diet for 12 weeks prior to the assessment of myocardial autophagy [55]. Their data revealed that the ratio of LC3B II/LC3B I was significantly increased in the heart under insulin resistance [55]. The authors suggested that autophagy activation might contribute to cardiac pathology in insulin resistance, although further analysis is required to support the status of autophagic flux in their mouse model. Recent studies demonstrated that myocardial autophagy is also altered in type 1 diabetes mellitus models, contributing to the development of diabetic cardiomyopathy [53,54]. In OVE26 and streptozotocin (STZ)-induced type 1 diabetic mice, autophagy was reported to be suppressed in the diabetic heart [54]. Moreover, autophagy suppression was found to be protective against diabetic cardiomyopathy, as evidenced by the attenuation of cardiac injury by Beclin1 and Atg16 deficiency but exacerbation of cardiac anomalies by Beclin1 overexpression [54]. However, autophagy suppression was suggested to be detrimental for cardiac homeostasis maintenance in OVE26 diabetic mice by another independent study [53]. Treatment with AMPK activator metformin rescued AMPK signaling and restored myocardial autophagy, resulting in the improvement of cardiac function [53]. Although it was claimed that the cardioprotective effect of metformin against diabetic cardiomyopathy was through autophagy restoration, it might not be the case given that metformin may act through other AMPK-mediated pathways. For example, AMPK can protect mitochondrial biogenesis and promote ATP-generating pathways [56], both of which may contribute to the cardioprotective effect of metformin in autophagy-independent manner.

4. Summary and conclusion

There is a growing need for the understanding of the correlation between metabolic syndrome and cardiac anomalies for the management of metabolic syndrome. Given that metabolic syndrome encompasses a cluster of cardiovascular risk factors, it is not surprising that patients with metabolic syndrome are more susceptible to cardiac geometric and functional anomalies. Accumulating independent clinical studies have shown that the presence of metabolic syndrome significantly enhanced morbidity and mortality of cardiac dysfunction in patients all over the world [23,26,27,29,30]. To better understand the mechanisms underlying metabolic syndrome-associated cardiac anomalies, multiple experimental models have been established [11,12,21,22]. In the Ossabaw swine model with metabolic syndrome, myocardial perfusion was significantly decreased with overt inflammation, oxidative stress, mitochondrial dysfunction and interstitial fibrosis [11]. In high fat diet-induced murine model of obesity and metabolic syndrome, cardiac output and cardiomyocyte contractile function were dramatically suppressed [12,22]. These models nicely recapitulate human models of obesity and metabolic syndrome to be used as a platform for the etiology and therapeutics of metabolic syndrome.

Over the past years, extensive studies have been focusing on understanding the role of myocardial autophagy under various pathological conditions, including ischemia/reperfusion [18], pressure overload-induced hypertrophy [19,48,49], and heart failure [20,49]. Although there is growing interest in the role of autophagy in the maintenance of cardiac homeostasis under various pathophysiological conditions, whether and exactly how autophagy is affected in metabolic syndrome-associated cardiac anomaly still remain elusive.

Up-to-date, the notion of disturbed autophagy in metabolic syndrome-associated cardiac injury is conceived by conflicting experimental data [11,12,21,22]. In the swine model of metabolic syndrome, myocardium displayed increased protein levels of Atg12–Atg5 along with decreased ULK1, Beclin1 and the LC3B II/I ratio [11]. In mouse models of high fat diet-induced metabolic syndrome, myocardial autophagy was unaffected although cardiac function was suppressed [21,22]. To the contrary, disturbed cardiac autophagic flux was reported in 45% high fat diet-induced model of obesity and metabolic syndrome, contributing to the cardiac geometric and functional anomalies [12]. Such discrepancy may be attributed to the fundamental differences (diet composition, animal gender and age) in experimental models [11,12,21,22].

In summary, although the current available information remains controversial, it is noteworthy that scientists are starting to appreciate the pivotal role of autophagy in the homeostasis of cardiac geometry and function under metabolic syndrome. Further studies are warranted to better understand the inconsistent data published using various animal models. For example, the contribution of various animal species and strain to cardiac autophagy under metabolic syndrome remains unknown. Second, the precise role of diet composition in cardiac autophagy under metabolic syndrome remains to be determined. Last but not the

Please cite this article as: S.Y. Ren, X. Xu, Role of autophagy in metabolic syndrome-associated heart disease, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2014.04.029

least, it is still unclear whether metabolic syndrome-induced changes in cardiac autophagy can be influenced by other factors, including age and gender. More in depth work is in need to clarify the precise interplay between cardiac autophagy and cardiac anomalies under metabolic syndrome. Ultimately, a better understanding of the role of cardiac autophagy in metabolic-induced cardiac anomalies should shed some lights towards a better management of cardiac injuries in patients with metabolic syndrome.

Acknowledgements

The work from the authors' laboratory was supported in part by a research project from Wyoming IDeA Network for Biomedical Research Excellence (INBRE, P20 GM103432) to XX. SYR was supported by a fellowship from the Wyoming Experimental Program to Stimulate Competitive Research (EPSCoR).

References

[1] J.P. Despres, Abdominal obesity as important component of insulin-resistance syndrome, Nutrition 9 (1993) 452–459.
[2] K.G. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation, Diabet. Med. 15 (1998) 539–553.
[3] B. Balkau, M.A. Charles, Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR), Diabet. Med. 16 (1999) 442–443.
[4] S.M. Grundy, J.I. Cleeman, S.R. Daniels, K.A. Donato, R.H. Eckel, B.A. Franklin, D.J. Gordon, R.M. Krauss, P.J. Savage, S.C. Smith Jr., J.A. Spertus, F. Costa, Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement, Circulation 112 (2005) 2735–2752, http://dx.doi.org/10.1161/CIRCULATIONAHA.105.169404.
[5] X. Xu, J. Ren, Cardiac stem cell regeneration in metabolic syndrome, Curr. Pharm. Des. 19 (2013) 4888–4892.
[6] E.S. Ford, W.H. Giles, W.H. Dietz, Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey, JAMA 287 (2002) 356–359.
[7] E.S. Ford, W.H. Giles, A.H. Mokdad, Increasing prevalence of the metabolic syndrome among U.S. adults, Diabetes Care 27 (2004) 2444–2449.
[8] A.S. Go, D. Mozaffarian, V.L. Roger, E.J. Benjamin, J.D. Berry, W.B. Borden, D.M. Bravata, S. Dai, E.S. Ford, C.S. Fox, S. Franco, H.J. Fullerton, C. Gillespie, S.M. Hailpern, J.A. Heit, V.J. Howard, M.D. Huffman, B.M. Kissela, S.J. Kittner, D.T. Lackland, J.H. Lichtman, L.D. Lisabeth, D. Magid, G.M. Marcus, A. Marelli, D.B. Matchar, D.K. McGuire, E.R. Mohler, C.S. Moy, M.E. Mussolino, G. Nichol, N.P. Paynter, P.J. Schreiner, P.D. Sorlie, J. Stein, T.N. Turan, S.S. Virani, N.D. Wong, D. Woo, M.B. Turner, Heart Disease and Stroke Statistics—2013 Update: a report from the American Heart Association, Circulation 127 (2013) e6–e245, http://dx.doi.org/10.1161/CIR.0b013e31828124ad.
[9] S.D. de Ferranti, K. Gauvreau, D.S. Ludwig, E.J. Neufeld, J.W. Newburger, N. Rifai, Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey, Circulation 110 (2004) 2494–2497, http://dx.doi.org/10.1161/01.CIR.0000145117.40114.C7.
[10] R. Weiss, J. Dziura, T.S. Burgert, W.V. Tamborlane, S.E. Taksali, C.W. Yeckel, K. Allen, M. Lopes, M. Savoye, J. Morrison, R.S. Sherwin, S. Caprio, Obesity and the metabolic syndrome in children and adolescents, N. Engl. J. Med. 350 (2004) 2362–2374, http://dx.doi.org/10.1056/NEJMoa031049.
[11] Z.L. Li, J.R. Woollard, B. Ebrahimi, J.A. Crane, K.L. Jordan, A. Lerman, S.M. Wang, L.O. Lerman, Transition from obesity to metabolic syndrome is associated with altered myocardial autophagy and apoptosis, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 1132–1141, http://dx.doi.org/10.1161/ATVBAHA.111.244061.
[12] X. Xu, Y. Hua, S. Nair, Y. Zhang, J. Ren, Akt2 knockout preserves cardiac function in high-fat diet-induced obesity by rescuing cardiac autophagosome maturation, J. Mol. Cell Biol. 5 (2013) 61–63, http://dx.doi.org/10.1093/jmcb/mjs055.
[13] X. Xu, J. Ren, Unmasking the janus faces of autophagy in obesity-associated insulin resistance and cardiac dysfunction, Clin. Exp. Pharmacol. Physiol. 39 (2012) 200–208, http://dx.doi.org/10.1111/j.1440-1681.2011.05638.x.
[14] N. Mizushima, T. Yoshimori, B. Levine, Methods in mammalian autophagy research, Cell 140 (2010) 313–326, http://dx.doi.org/10.1016/j.cell.2010.01.028.
[15] X. Qu, Z. Zou, Q. Sun, K. Luby-Phelps, P. Cheng, R.N. Hogan, C. Gilpin, B. Levine, Autophagy gene-dependent clearance of apoptotic cells during embryonic development, Cell 128 (2007) 931–946, http://dx.doi.org/10.1016/j.cell.2006.12.044.
[16] A. Nakai, O. Yamaguchi, T. Takeda, Y. Higuchi, S. Hikoso, M. Taniike, S. Omiya, I. Mizote, Y. Matsumura, M. Asahi, K. Nishida, M. Hori, N. Mizushima, K. Otsu, The role of autophagy in cardiomyocytes in the basal state and in response to hemodynamic stress, Nat. Med. 13 (2007) 619–624, http://dx.doi.org/10.1038/nm1574.
[17] X. Xu, N.D. Roe, M.C. Weiser-Evans, J. Ren, Inhibition of mammalian target of rapamycin with rapamycin reverses hypertrophic cardiomyopathy in mice with cardiomyocyte-specific knockout of PTEN, Hypertension 63 (2014) 729–739, http://dx.doi.org/10.1161/HYPERTENSIONAHA.113.02526.
[18] Y. Matsui, S. Kyoi, H. Takagi, C.P. Hsu, N. Hariharan, T. Ago, S.F. Vatner, J. Sadoshima, Molecular mechanisms and physiological significance of autophagy during myocardial ischemia and reperfusion, Autophagy 4 (2008) 409–415.
[19] X. Xu, Y. Hua, S. Nair, R. Bucala, J. Ren, Macrophage migration inhibitory factor deletion exacerbates pressure overload-induced cardiac hypertrophy through mitigating autophagy, Hypertension 63 (2014) 490–499, http://dx.doi.org/10.1161/HYPERTENSIONAHA.113.02219.
[20] X. Xu, R. Bucala, J. Ren, Macrophage migration inhibitory factor deficiency augments doxorubicin-induced cardiomyopathy, J. Am. Heart Assoc. 2 (2013) e000439, http://dx.doi.org/10.1161/JAHA.113.000439.
[21] M. Cui, H. Yu, J. Wang, J. Gao, J. Li, Chronic caloric restriction and exercise improve metabolic conditions of dietary-induced obese mice in autophagy correlated manner without involving AMPK, J. Diabetes Res. 2013 (2013) 852754, http://dx.doi.org/10.1155/2013/852754.
[22] S. Lancel, D. Montaigne, X. Marechal, C. Marciniak, S.M. Hassoun, B. Decoster, C. Ballot, C. Blazejewski, D. Corseaux, B. Lescure, R. Motterlini, R. Neviere, Carbon monoxide improves cardiac function and mitochondrial population quality in a mouse model of metabolic syndrome, PLoS One 7 (2012) e41836, http://dx.doi.org/10.1371/journal.pone.0041836.
[23] H.M. Lakka, D.E. Laaksonen, T.A. Lakka, L.K. Niskanen, E. Kumpusalo, J. Tuomilehto, J. T. Salonen, The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men, JAMA 288 (2002) 2709–2716.
[24] H.E. Resnick, K. Jones, G. Ruotolo, A.K. Jain, J. Henderson, W. Lu, B.V. Howard, Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic American Indians: the Strong Heart Study, Diabetes Care 26 (2003) 861–867.
[25] B. Isomaa, P. Almgren, T. Tuomi, B. Forsen, K. Lahti, M. Nissen, M.R. Taskinen, L. Groop, Cardiovascular morbidity and mortality associated with the metabolic syndrome, Diabetes Care 24 (2001) 683–689.
[26] M.P. Stern, K. Williams, C. Gonzalez-Villalpando, K.J. Hunt, S.M. Haffner, Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care 27 (2004) 2676–2681.
[27] H.E. Park, S.Y. Choi, M. Kim, Association of epicardial fat with left ventricular diastolic function in subjects with metabolic syndrome: assessment using 2-dimensional echocardiography, BMC Cardiovasc. Disord. 14 (2014) 3, http://dx.doi.org/10.1186/1471-2261-14-3.
[28] H. Turhan, A.S. Yasar, J. Yagmur, E. Kurtoglu, E. Yetkin, The impact of metabolic syndrome on left ventricular function: evaluated by using the index of myocardial performance, Int. J. Cardiol. 132 (2009) 382–386, http://dx.doi.org/10.1016/j.ijcard.2007.12.007.
[29] H. Masugata, S. Senda, F. Goda, Y. Yoshihara, K. Yoshikawa, N. Fujita, H. Daikuhara, H. Nakamura, T. Taoka, M. Kohno, Left ventricular diastolic dysfunction as assessed by echocardiography in metabolic syndrome, Hypertens. Res. 29 (2006) 897–903, http://dx.doi.org/10.1291/hypres.29.897.
[30] H.P. Gong, H.W. Tan, N.N. Fang, T. Song, S.H. Li, M. Zhong, W. Zhang, Y. Zhang, Impaired left ventricular systolic and diastolic function in patients with metabolic syndrome as assessed by strain and strain rate imaging, Diabetes Res. Clin. Pract. 83 (2009) 300–307, http://dx.doi.org/10.1016/j.diabres.2008.10.018.
[31] Y.C. Hwang, J.H. Jee, M. Kang, E.J. Rhee, J. Sung, M.K. Lee, Metabolic syndrome and insulin resistance are associated with abnormal left ventricular diastolic function and structure independent of blood pressure and fasting plasma glucose level, Int. J. Cardiol. 159 (2012) 107–111, http://dx.doi.org/10.1016/j.ijcard.2011.02.039.
[32] A.F. Ceylan-Isik, M.R. Kandadi, X. Xu, Y. Hua, A.J. Chicco, J. Ren, S. Nair, Apelin administration ameliorates high fat diet-induced cardiac hypertrophy and contractile dysfunction, J. Mol. Cell. Cardiol. 63 (2013) 4–13, http://dx.doi.org/10.1016/j.yjmcc.2013.07.002.
[33] Y. Hua, Y. Zhang, J. Dolence, G.P. Shi, J. Ren, S. Nair, Cathepsin K knockout mitigates high-fat diet-induced cardiac hypertrophy and contractile dysfunction, Diabetes 62 (2013) 498–509, http://dx.doi.org/10.2337/db12-0350.
[34] B. Levine, D.J. Klionsky, Development by self-digestion: molecular mechanisms and biological functions of autophagy, Dev. Cell 6 (2004) 463–477.
[35] X. Xu, B.D. Pacheco, L. Leng, R. Bucala, J. Ren, Macrophage migration inhibitory factor plays a permissive role in the maintenance of cardiac contractile function under starvation through regulation of autophagy, Cardiovasc. Res. 99 (2013) 412–421, http://dx.doi.org/10.1093/cvr/cvt116.
[36] M. Sun, M. Ouzounian, G. de Couto, M. Chen, R. Yan, M. Fukuoka, G. Li, M. Moon, Y. Liu, A. Gramolini, G.J. Wells, P.P. Liu, Cathepsin-L ameliorates cardiac hypertrophy through activation of the autophagy-lysosomal dependent protein processing pathways, J Am Heart Assoc 2 (2013) e000191, http://dx.doi.org/10.1161/JAHA.113.000191.
[37] S.J. Goldman, Y. Zhang, S. Jin, Autophagic degradation of mitochondria in white adipose tissue differentiation, Antioxid. Redox Signal. 14 (2011) 1971–1978, http://dx.doi.org/10.1089/ars.2010.3777.
[38] C. He, D.J. Klionsky, Regulation mechanisms and signaling pathways of autophagy, Annu. Rev. Genet. 43 (2009) 67–93, http://dx.doi.org/10.1146/annurev-genet-102808-114910.
[39] Y. Zhang, X. Xu, J. Ren, MTOR overactivation and interrupted autophagy flux in obese hearts: a dicey assembly? Autophagy 9 (2013) 939–941, http://dx.doi.org/10.4161/auto.24398.
[40] C.H. Jung, S.H. Ro, J. Cao, N.M. Otto, D.H. Kim, mTOR regulation of autophagy, FEBS Lett. 584 (2010) 1287–1295, http://dx.doi.org/10.1016/j.febslet.2010.01.017.
[41] Y. Hua, Y. Zhang, A.F. Ceylan-Isik, L.E. Wold, J.M. Nunn, J. Ren, Chronic Akt activation accentuates aging-induced cardiac hypertrophy and myocardial contractile dysfunction: role of autophagy, Basic Res. Cardiol. 106 (2011) 1173–1191, http://dx.doi.org/10.1007/s00395-011-0222-8.

Please cite this article as: S.Y. Ren, X. Xu, Role of autophagy in metabolic syndrome-associated heart disease, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2014.04.029

[42] X. Xu, L.K. Hueckstaedt, J. Ren, Deficiency of insulin-like growth factor 1 attenuates aging-induced changes in hepatic function: role of autophagy, J. Hepatol. 59 (2013) 308–317, http://dx.doi.org/10.1016/j.jhep.2013.03.037.
[43] C.H. Lee, K. Inoki, K.L. Guan, mTOR pathway as a target in tissue hypertrophy, Annu. Rev. Pharmacol. Toxicol. 47 (2007) 443–467, http://dx.doi.org/10.1146/annurev.pharmtox.47.120505.105359.
[44] S.L. Cai, A.R. Tee, J.D. Short, J.M. Bergeron, J. Kim, J. Shen, R. Guo, C.L. Johnson, K. Kiguchi, C.L. Walker, Activity of TSC2 is inhibited by AKT-mediated phosphorylation and membrane partitioning, J. Cell Biol. 173 (2006) 279–289, http://dx.doi.org/10.1083/jcb.200507119.
[45] N. Hariharan, Y. Maejima, J. Nakae, J. Paik, R.A. Depinho, J. Sadoshima, Deacetylation of FoxO by Sirt1 plays an essential role in mediating starvation-induced autophagy in cardiac myocytes, Circ. Res. 107 (2010) 1470–1482, http://dx.doi.org/10.1161/CIRCRESAHA.110.227371.
[46] R. Guo, J. Ren, Deficiency in AMPK attenuates ethanol-induced cardiac contractile dysfunction through inhibition of autophagosome formation, Cardiovasc. Res. 94 (2012) 480–491, http://dx.doi.org/10.1093/cvr/cvs127.
[47] N.R. Brady, A. Hamacher-Brady, H. Yuan, R.A. Gottlieb, The autophagic response to nutrient deprivation in the hl-1 cardiac myocyte is modulated by Bcl-2 and sarco/endoplasmic reticulum calcium stores, FEBS J. 274 (2007) 3184–3197, http://dx.doi.org/10.1111/j.1742-4658.2007.05849.x.
[48] D.J. Cao, Z.V. Wang, P.K. Battiprolu, N. Jiang, C.R. Morales, Y. Kong, B.A. Rothermel, T. G. Gillette, J.A. Hill, Histone deacetylase (HDAC) inhibitors attenuate cardiac hypertrophy by suppressing autophagy, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 4123–4128, http://dx.doi.org/10.1073/pnas.1015081108.
[49] H. Zhu, P. Tannous, J.L. Johnstone, Y. Kong, J.M. Shelton, J.A. Richardson, V. Le, B. Levine, B.A. Rothermel, J.A. Hill, Cardiac autophagy is a maladaptive response to hemodynamic stress, J. Clin. Invest. 117 (2007) 1782–1793, http://dx.doi.org/10.1172/JCI27523.
[50] R. Guo, Y. Zhang, S. Turdi, J. Ren, Adiponectin knockout accentuates high fat diet-induced obesity and cardiac dysfunction: role of autophagy, Biochim. Biophys. Acta 1832 (2013) 1136–1148, http://dx.doi.org/10.1016/j.bbadis.2013.03.013.
[51] C. He, M.C. Bassik, V. Moresi, K. Sun, Y. Wei, Z. Zou, Z. An, J. Loh, J. Fisher, Q. Sun, S. Korsmeyer, M. Packer, H.I. May, J.A. Hill, H.W. Virgin, C. Gilpin, G. Xiao, R. Bassel-Duby, P.E. Scherer, B. Levine, Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis, Nature 481 (2012) 511–515, http://dx.doi.org/10.1038/nature10758.
[52] S. Sciarretta, P. Zhai, D. Shao, Y. Maejima, J. Robbins, M. Volpe, G. Condorelli, J. Sadoshima, Rheb is a critical regulator of autophagy during myocardial ischemia: pathophysiological implications in obesity and metabolic syndrome, Circulation 125 (2012) 1134–1146, http://dx.doi.org/10.1161/CIRCULATIONAHA.111.078212.
[53] Z. Xie, K. Lau, B. Eby, P. Lozano, C. He, B. Pennington, H. Li, S. Rathi, Y. Dong, R. Tian, D. Kem, M.H. Zou, Improvement of cardiac functions by chronic metformin treatment is associated with enhanced cardiac autophagy in diabetic OVE26 mice, Diabetes 60 (2011) 1770–1778, http://dx.doi.org/10.2337/db10-0351.
[54] X. Xu, S. Kobayashi, K. Chen, D. Timm, P. Volden, Y. Huang, J. Gulick, Z. Yue, J. Robbins, P.N. Epstein, Q. Liang, Diminished autophagy limits cardiac injury in mouse models of type 1 diabetes, J. Biol. Chem. 288 (2013) 18077–18092, http://dx.doi.org/10.1074/jbc.M113.474650.
[55] K.M. Mellor, J.R. Bell, M.J. Young, R.H. Ritchie, L.M. Delbridge, Myocardial autophagy activation and suppressed survival signaling is associated with insulin resistance in fructose-fed mice, J. Mol. Cell. Cardiol. 50 (2011) 1035–1043, http://dx.doi.org/10.1016/j.yjmcc.2011.03.002.
[56] R.M. Reznick, G.I. Shulman, The role of AMP-activated protein kinase in mitochondrial biogenesis, J. Physiol. 574 (2006) 33–39, http://dx.doi.org/10.1113/jphysiol.2006.109512.

Please cite this article as: S.Y. Ren, X. Xu, Role of autophagy in metabolic syndrome-associated heart disease, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2014.04.029