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Autophagy as an Emerging Target in Cardiorenal Metabolic Disease: from Pathophysiology to Management

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Abstract

Although advances in medical technology and health care have improved the early diagnosis and management for cardiorenal metabolic disorders, the prevalence of obesity, insulin resistance, diabetes, hypertension, dyslipidemia, and kidney disease remains high. Findings from numerous population-based studies, clinical trials, and experimental evidence have consolidated a number of theories for the pathogenesis of cardiorenal metabolic anomalies including resistance to the metabolic action of insulin, abnormal glucose and lipid metabolism, oxidative and nitrosative stress, endoplasmic reticulum (ER) stress, apoptosis, mitochondrial damage, and inflammation. Accumulating evidence has recently suggested a pivotal role for proteotoxicity, the unfavorable effects of poor protein quality control, in the pathophysiology of metabolic dysregulation and related cardiovascular complications. The ubiquitin-proteasome system (UPS) and autophagy-lysosomal pathways, two major although distinct cellular clearance machineries, govern protein quality control by degradation and clearance of long-lived or damaged proteins and organelles. Ample evidence has depicted an important role for protein quality control, particularly autophagy, in the maintenance of metabolic homeostasis. To this end, autophagy offers promising targets for novel strategies to prevent and treat cardiorenal metabolic diseases. Targeting autophagy using pharmacological or natural agents exhibits exciting new strategies for the growing problem of cardiorenal metabolic disorders.

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I. Introduction - Definitions and Differential Diagnosis

a. Nomenclature (metabolic syndrome, cardiometabolic syndrome, cardiorenal metabolic syndrome), NIH/ADA diagnostic criteria

Ample evidence has suggested that risk factors for cardiovascular disease (CVD) often cluster together, in the form of obesity, insulin resistance, type 2 diabetes mellitus, dyslipidemia and hypertension (Alberti, et al., 2009; Alberti, Zimmet, & Shaw, 2005). The initial definition of "Syndrome X" encompassed the presence of insulin resistance/ hyperinsulinemia, hypertension, glucose intolerance, and metabolic dyslipidemia [e.g., increased very-low-density lipoprotein (VLDL) and decreased HDL cholesterol (HDL-c)] (Reaven, 1988, 1993). Hyperuricemia, angina and elevated plasminogen activator inhibitor 1 (PAI-1) were later included as additional features of this syndrome (Reaven, 1993), referred to as the "metabolic syndrome" or "cardiometabolic syndrome" (Invitti, Gilardini, & Viberti, 2004; Ren, Pulakat, Whaley-Connell, & Sowers, 2010; Shulman & Mangelsdorf, 2005; Whaley-Connell & Sowers, 2014). Since its first appearance in the medical vernacular three decades ago, the general health impact of this constellation of metabolic disorders is increasingly recognized (Govindarajan, Whaley-Connell, Mugo, Stump, & Sowers, 2005). In 2005, the American Heart Association (AHA)/National Heart, Lung and Blood Institute (NHLBI) revised the definition of metabolic syndrome and required presence of three out of the five following criteria: elevated waist circumference (≥ 102 cm in males and ≥ 88 cm in females), triglycerides ≥ 150 mg/dl, and HDL-c < 40 mg/dl in men and < 50 mg/dl in women, elevated blood pressure ≥ 130/85 mmHg and elevated fasting glucose >100 mg/dl (Grundy, et al, 2006). Here, ethnic-specific waist circumferences should be taken into account when using this criterion in addition to adjusting impaired fasting glucose > 100 mg/dl, in compliance with the International Diabetes Federation (IDF) guidelines. These efforts allow us to handle the cardiorenal metabolic syndrome as a set of easily obtainable measures to identify individuals with a high risk for CVD and type 2 diabetes mellitus. The growing prevalence of obesity and diabetes continues to undermine the management of CVD (Alberti, et al, 2005; Rask Larsen, Dima, Correll, & Manu, 2018). A more comprehensive view of obesity is judged based on waist circumference as opposed to body mass index (BMI) in the Harmonization definition of cardiorenal metabolic syndrome (Alberti, et al., 2005; Smith & Ryckman, 2015). Additional evidence suggests that the waist-to-height ratio may be superior to both waist circumference and BMI (Ashwell, Gunn, & Gibson, 2012). Despite wide acknowledgement that intensive clinical management improves CVD outcomes, many patients with cardiorenal metabolic syndrome still face suboptimal risk factor management (Rask Larsen, et al., 2018).

b. Epidemiology and the exclusion of other endocrine disorders

The National Health and Nutrition Examination Survey (NHANES) survey suggested an age-adjusted prevalence of 22.9% of cardiorenal metabolic syndrome between 2009 and

2010, among those 20 years or older in the United States (Beltran-Sanchez, Harhay, Harhay, & McElligott, 2013). Data from the International Diabetes Federation (IDF) suggested that 25% of worldwide adult population suffer from the syndrome with 5% in those exhibiting normal weight, 22% being overweight, and 60% being obese (J. Li & Pfeffer, 2016). The prevalence of cardiorenal metabolic syndrome is much higher in developed countries compared with developing countries, although westernization of developing countries (high calorie diet and low physical activity) saw a quick rise in cardiorenal metabolic syndrome recently (Naidu, Ponnampalvanar, Kamaruzzaman, & Kamarulzaman, 2017). Moreover, a higher rate was found in urban compared with rural populations (Pradeepa, et al., 2016). A positive correlation is also present with aging. The Lifestyle Interventions and Independence for Elders Study reported a prevalence of cardio renal metabolic syndrome of nearly 50% in community-dwelling sedentary adults aged 70 to 89 years (Botoseneanu, et al., 2015).

c. Evaluation of clinical features of cardiorenal metabolic syndrome

While the actual diagnosis of the cardiorenal metabolic syndrome has little therapeutic relevance other than managing the individual components, attenuating CVD risk is a main drive in clinical practice. Individual components of cardiorenal metabolic syndrome serve as independent risk factors for the overall prevalence of cardiovascular disease (Fig. 1). Presence of concurrent risk factors drastically elevates rates and severity of cardiovascular diseases (Z. L. Li, et al., 2012; Neeland, Poirier, & Despres, 2018). The optimal management for individual components such as blood pressure, lipid, or HA1c goals differ in individuals based on age, ethnicity and the presence of confounding comorbidities (Vaughan & Mattison, 2016). For example, weight control lowers the overall risk of insulin resistance, type 2 diabetes, hypertension, dyslipidemia and albuminuria (Bassuk & Manson, 2005) although control of dyslipidemia has little impact on body weight, blood pressure or glycemic control. An additional consideration is the impact that cardiorenal metabolic abnormalities may predispose patients to other anomalies such as cognitive decline (C. Li & Lumey, 2016; Vaughan & Mattison, 2016). Thus, it is imperative to elucidate the precise mechanism behind the CVD complications of cardiorenal metabolic syndrome including cardiac remodeling, microvascular dysfunction, heart failure, albuminuria, coronary atherosclerosis, calcification and premature senescence (Di Lullo, Bellasi, Russo, Cozzolino, & Ronco, 2017; Ludwig, 2016). Earlier conceptualizations of cardiorenal metabolic syndrome mainly focused on obesity with insulin resistance as a core feature. A large volume of clinical and experimental evidence depicted the pathophysiological mechanisms of cardiorenal metabolic syndrome including identification of genes responsible for syndromic or non-syndromic monogenic oligogenic or polygenic anomalies and interplays among genetic and epigenetic factors (Whaley-Connell & Sowers, 2014; Y. Zhang & Ren, 2016). More recent findings have depicted an essential role for autophagy, a cellular process of degrading long-lived, injured proteins and organelles (Mizushima, 2018; S. Yan, Huda, Khambu, & Yin, 2017), in the pathogenesis of cardiorenal metabolic syndrome. Dysregulated autophagy is present in multiple metabolic anomalies including obesity, insulin resistance, diabetes mellitus and dyslipidemia (K. H. Kim & Lee, 2014; Lamb, Dooley, & Tooze, 2013; Marasco & Linnemann, 2018; Y. Zhang, Sowers, & Ren, 2018). While advances in the understanding of the etiology of this complex disorder have been made (Rask Larsen, et al., 2018; Whaley-Connell & Sowers, 2014; Y. Zhang & Ren, 2016;

Y. Zhang, et al., 2018), risk reduction remains suboptimal for those high-risk populations, warranting novel therapeutic strategies.

II. Autophagy: Biochemistry, Cell Biology and Regulation of Autophagy

a. Biochemistry, molecular overview, regulation and functionality of autophagy

The ubiquitin-proteasome system (UPS) and autophagy-lysosome systems are the two main proteolytic pathways in eukaryotic cells to govern protein quality. Unlike the UPS pathway, the autophagy-lysosome mechanism participates in the bulk degradation of cytoplasmic organelles and protein aggregates which cannot be degraded by the UPS system (Levine & Klionsky, 2004, 2017; Mizushima, 2018). To-date, three types of autophagy are reported to remove long-lived, damaged and aggregated cellular components including macroautophagy, chaperone-mediated autophagy (CMA) and microautophagy (Levine & Klionsky, 2004, 2017; Mizushima, 2018). Microautophagy involves invagination of lysosomal or endosomal membranes to engulf cargo content. CMA employs a pentapeptide KFERQ motif and heat shock chaperon to transport cargos into lysosome. Macroautophagy (or autophagy) involves formation of double-membraned autophagosomes to sequester cargo contents and fusion with autolysosomes for degradation (Fig. 2). In autophagy, the double-membrane autophagosomes are capable of identifying and sequestering cellular cargo tagged by autophagy adaptors (e.g., sequestosome 1 [p62/SQSTM1], neighbor of Brca 1 [NBR1] and optineurin) (Stolz, Ernst, & Dikic, 2014). Cargo recognition depends on ubiquitination although non-ubiquitinated cargo may also be cleared under certain circumstances (Levine & Klionsky, 2004). Four steps have been identified in the autophagic process including initiation, engulfment of cargo by a double-membrane structure, formation of autophagolysosomes via the fusion of autophagosome and lysosome, and the final process of lysosomal degradation by acid hydrolases resulting in the recycling of lysosomal contents (Fig. 2) (Levine & Klionsky, 2004). Specific types of autophagy exist mainly depending on the selectivity of cargo delivery modality including glyophagy (glycogen), lipophagy (lipids) and mitophagy (mitochondria) (Evans, Sergin, Zhang, & Razani, 2017; Gatica, Lahiri, & Klionsky, 2018). The formation of isolation membrane begins at phagophore assembly sites including the Golgi, ER, endosomes, and mitochondria. Following the formation of isolated membranes, ubiquitin-like conjugation cascades Atg5-Atg12-Atg16L and Atg4-Atg3-LC3-II catalyze membrane elongation to generate autophagosomes. Atg12 becomes conjugated to Atg5 by an ubiquitination-like reaction through Atg7 and Atg10 prior to the association of Atg16L to the Atg12-Atg5 complex, producing the Atg5-Atg12- Atg16L complex (Nakatogawa & Ohsumi, 2014). The microtubule-associated protein 1 light chain 3 (LC3) is then cleaved at C-terminal by Atg4. The cytosolic LC3-I and phosphatidylethanolamine (PE) are connected by Atg3 and Atg7 to yield the lipidated LC3-II on autophagosomal membranes (Medvedev, Hildt, & Ploen, 2017). Then p62 directs ubiquitinated cargo to autophagosomal compartments (Taniguchi, Yamachika, He, & Karin, 2016), prior to the conjugation with the lysosome for the autophagolysosomes for degradation and recycling (Medvedev, et al., 2017).

Autophagy is essential to cellular homeostasis and survival through quality control of amino acid pools and energy metabolism (Cheng, Ren, Hait, & Yang, 2013; Ren & Anversa, 2015;

Rybstein, Bravo-San Pedro, Kroemer, & Galluzzi, 2018). With stress stimuli including nutrient starvation, hypoxia, oxidative stress, DNA damage, protein aggregates, and intracellular pathogens, autophagy is induced to preserve cellular integrity and physiological homeostasis (C. He & Klionsky, 2009). Autophagy is induced under starvation by posttranslational modifications and protein-protein interactions to release amino acids and fatty acids favoring cell survival (K. H. Kim & Lee, 2014; X. Xu, Pacheco, Leng, Bucala, & Ren, 2013). Mammalian target of rapamycin (mTOR) is the most predominant regulator of autophagy involving 2 complexes - MTORC1 and MTORC2. MTORC1, consisting of mTOR, raptor and mLST8, is rapamycin-sensitive. MTORC2, containing mTOR, rictor, mLST8, PRAS40, and DEPTOR, is rapamycin-insensitive (C. H. Jung, Ro, Cao, Otto, & Kim, 2010; Sciarretta, Forte, Frati, & Sadoshima, 2018). By phosphorylating unc-51 like kinase-1 (ULK1, the orthologue of mammalian Atg1), mTOR forms a complex with ULK1, Atg13 and FIP200, thus inhibiting autophagy (C. H. Jung, et al., 2010). MTORC1 complex (referred to as mTOR) may suppress autophagy through phosphorylation and thus inactivation of ULK/Atg1 and ATG13/Atg13, essential steps in the activation of autophagy. On the other hand, MTORC2 comp lex regulates cell shape, metabolism and autophagy. MTOR functions as a hub to integrate metabolic signals including insulin, growth factors, and cellular energy. One of the well-defined pathways intersecting with MTOR in the regulation of metabolism, growth and longevity is the insulin- insulin like growth factor 1 (IGF1) pathway (Kenyon, 2010). Upon activation of the insulin-IGF-1 cascade, class I phosphatidylinositide-3-kinase (PI3K) is activated to turn on PIP2, to recruit Akt to plasma membranes, where it is phosphorylated by 3-phosphoinositide dependent protein kinase 1/2 (PDPK1/2). Akt next regulates the heterodimeric tuberous sclerosis complex (TSC), which inhibits MTOR through suppression of Rheb (Y. Zhang, et al., 2003). Therefore, the TSC-Rheb-MTOR cascade represents a major signaling axis for growth and autophagy.

Autophagy is turned on by the energy sensor AMP-dependent protein kinase (AMPK), and activation of the ULK/Atg1 initiation complex. Beclin 1 then forms a complex with the PI3K-complex (class III phosphatidylinositol-3-kinase, Vps34, p150, Atg14) along with ULK1/2-complex to generate a phosphatidylinositol-3-phosphate (PI3P)-enriched environment, for nucléation of the isolation membrane. AMPK is sensitive to AMP levels, and may be activated by upstream kinases such as STK11/LKB1 and CaMKK2/CaMKKß (Ca^{2+}/calmodulin-dependent protein kinase kinase 2ß) (Burkewitz, Zhang, & Mair, 2014). Among these AMPK-upstream kinases, STK11/LKB1 is constitutively active while CaMKK2 is responsive to changes in intracellular Ca^{2+} levels. AMPK also promotes autophagy via phosphorylation of the MTORC1 subunit RPTOR/raptor or dephosphorylation of TSC1/2, resulting in mTOR inhibition. Moreover, AMPK and MTOR may be phosphorylated by ULK/Atg1, offering in a feedback control mechanism of autophagy (Lapierre, Kumsta, Sandri, Ballabio, & Hansen, 2015). A simplified scheme illustrates these autophagy regulatory processes (Fig. 3)

b. Autophagy in human diseases

Autophagy serves as an indispensable process for cellular homeostasis involved in immunity, inflammation, and metabolism (Choi, Ryter, & Levine, 2013). Either excessive or defective autophagy may be associated with human metabolic diseases (Sinha-Hikim, Sinha-

Hikim, & Friedman, 2017), indicating the unique role of autophagy in the regulation of metabolic homeostasis.

Cardiovascular Diseases: Dysregulated autophagy is commonly seen in cardiovascular diseases including cardiomyopathies, cardiac hypertrophy, ischemia-reperfusion injury, atherosclerosis, diabetes, and drug-induced cardiotoxicity (Bartlett, Trivedi, & Pulinilkunnil, 2017; Evans, Jeong, Zhang, & Razani, 2018; Evans, et al., 2017; X. Xu, Bucala, & Ren, 2013). In ischemia-reperfusion, autophagy is protective during early ischemia, while excessive autophagy is detrimental during reperfusion (H. Ma, Guo, Yu, Zhang, & Ren, 2011; W. J. Yan, Dong, & Xiong, 2013). Basal autophagy is deemed beneficial for cardiac hypertrophy whereas excessive autophagy may promote pathological cardiac remodeling and myopathies (J. Li & Cai, 2015; Nishida & Otsu, 2016). Thus understanding the functional role of autophagy in various cardiovascular diseases and if manipulation of autophagy offers therapeutic benefits are a major focus of research in recent years (Lampert & Gustafsson, 2018; Ren & Taegtmeyer, 2015). In addition, X-linked deficiency in autophagosome-lysosome fusion protein - lysosome-associated membrane protein 2 (LAMP2), leads to Danon's cardiomyopathy with mitochondrial dysfunction and elevated autophagosomes (Rowland, Sweet, Mestroni, & Taylor, 2016). Along the same line, facilitated autophagy is evident in macrophages from atherosclerotic plaques where autophagy is capa ble of stabilizing atherosclerotic plaques by retarding apoptosis and necrosis (De Meyer, et al., 2015; Evans, et al., 2018; Grootaert, et al., 2018). Although consensus exists that autophagy is an essential cellular quality control pathway in cardiovascular homeostasis, its precise role in disease pathology remains controversial.

Cancer: Autophagy participates in the initiation, progression, therapeutic efficacy and prognosis of cancer, demonstrating a dual regulation of tumor development (Choi, et al., 2013; Rybstein, et al., 2018). Autophagy might promote cancer cell survival or cancer cell death (Russo & Russo, 2018). Altered autophagy and chromosomal autophagy genes are found in various forms of cancer (S. He & Liang, 2015; Rybstein, et al., 2018). For example, monoallelic disruption of *Beclin 1* on chromosome 17q21 is found in human breast, ovarian, and prostate tumors (Negri, et al., 2010). Homozygous deletion of *Becn1* in mice leads to embryonic lethality, whereas the monoallelic deletion *(Beclin1+/−)* promotes spontaneous tumorigenesis, favoring a role for Beclin 1 as a haploinsufficient tumor-suppressor (Yue, Jin, Yang, Levine, & Heintz, 2003). The tumor-suppressing function has been confirmed for multiple autophagy-associated proteins (e.g., Uvrag, Bif1, Atg4C, Atg5, and Atg7) (J. Liu & Debnath, 2016). Consistently, classical tumor suppressing proteins including tensin homolog deleted in chromosome 10 (PTEN), TSC1/2, liver kinase B1 (LKB1), and p53 directly promote autophagy (Choi, et al., 2013). Autophagy is speculated to provide an anti-carcinogenic action by safeguarding against metabolic stress through homeostatic turnover of mitochondria and protein aggregates (J. Liu & Debnath, 2016). However, the apparent pro-survival role of autophagy for cancer cells suggests the necessity for a thorough understanding of the dichotomy roles of autophagy in cancer biology in order to develop anti-cancer drugs capable of inducing or blocking autophagy in a tissue- and time-dependent manner (Russo & Russo, 2018).

Metabolic Diseases: Autophagy plays an essential role in metabolic diseases including obesity, insulin resistance, diabetes mellitus, and steatohepatitis through not only protein quality control but also release of amino acids, lipids, and other metabolic precursors (Madrigal-Matute & Cuervo, 2016; Sinha, Singh, & Yen, 2017; Y. Zhang, et al., 2018). Dysregulated autophagy promotes metabolic anomalies as evidenced by increased adiposity, insulin resistance, and hepatic storage of triglycerides with genetic deletion of autophagy genes, depic ting a role for autophagy in lipid metabolism (C. He, et al., 2013; Jaber, et al., 2012; Lim, et al., 2014; Y. Liu, et al., 2016; Madrigal-Matute & Cuervo, 2016; Settembre, De Cegli, et al., 2013). Genetic deletion of the autophagy gene Atg7 in the brain decreases food intake (Kaushik, et al., 2011). It is suggested that deletion of autophagy gene may affect metabolic phenotype in an organ specific-manner, as adipose-specific deletion of autophagy promotes insulin sensitivity and metabolic homeostasis (R. Singh, et al., 2009). On the other side of the coin, aberrant (increased or decreased) autophagy was found in various organs (such as liver, adipose tissue, heart and pancreas) in obesity, insulin resistance and diabetes (E. Chang, et al., 2015; H. H. Chang, et al., 2017; Ebato, et al., 2008; C. He, et al., 2012; Hsu, et al., 2016), the effect of which might be alleviated by lipid lowering agents and life style modification such as physical exercise or intermittent fasting (E. Chang, et al., 2015; C. He, et al., 2012; H. Liu, et al., 2017).

Aging: Aging leads to accumulation of lipofuscin pigments and ubiquitinated protein aggregates along with defective autophagy (Cheng, et al., 2013; Nair & Ren, 2012). Evidence from mice and roundworm Caenorhabditis elegans suggests that autophagy induction prolongs lifespan (Rubinsztein, Marino, & Kroemer, 2011). Furthermore, analysis of gene expression in the brain revealed loss of autophagy with aging. Dietary restriction, a classical way to facilitate autophagy, is perhaps the most robust manipulation to prolong healthy lifespan (Kapahi, Kaeberlein, & Hansen, 2016). More evidence suggests that lysosomal defect is associated with aging-associated pathologies including Parkinson's and Alzheimer's disease, as well as shortened lifespan (Shi, Guberman, & Kirshenbaum, 2017). Likewise, targeting lysosomal function has shown promises in promoting longevity (Carmona-Gutierrez, Hughes, Madeo, & Ruckenstuhl, 2016).

III. Pathophysiology of the Cardiorenal Metabolic Syndrome

To better decipher the role of autophagy regulation in cardiorenal metabolic syndrome, it is pertinent to understand the pathophysiology of this medical problem. To date, a number of theories have been proposed describing the onset and progression of cardiorenal metabolic syndrome including excessive caloric intake, oxidative stress, inflammation, insulin resistance, hypertension, dyslipidemia, as well as genetic and epigenetic factors (as depicted in Fig. 1) (da Silva, Rodrigues, Rebelo, Miranda, & Soveral, 2018; Dommermuth & Ewing, 2018). Recent findings suggest that extracellular vesicles from various origins, including endothelial, smooth muscle, skeletal muscle, hepatocytes, adipocytes, macrophages, and microbiota may also serve as bioeffectors for metabolic disorders (Martinez & Andriantsitohaina, 2017; van Greevenbroek, Schalkwijk, & Stehouwer, 2016). Nonetheless, little is known as to why this constellation of metabolic disorders contributes to CVD beyond the sum of its individual components.

a. Insulin resistance and hypertension

Despite the predominant role for obesity and type 2 diabetes in the pathogenesis of cardiorenal metabolic syndrome, insulin resistance, a nexus among components of the syndrome with coexistence of hyperinsulinemia, obesity, dyslipidemia, albuminuria and hypertension, is considered the cardinal feature of this syndrome (Fig. 1) (Alberti, et al., 2005; Reaven, 1993). Insulin resistance triggers inappropriate activation of renin-angiotensin aldosterone system (RAAS) and oxidative stress, and serves as a common denominator for various components of the syndrome (J. A. Kim, Wei, & Sowers, 2008). Ample experimental evidence has depicted a pivotal role for insulin and insulin signaling in metabolism, cell growth, and survival through activation of mitogen-activated protein kinases (MAPKs) and PI3K as well as their downstream signaling cascades (Fu, Wang, & Xiang, 2017; Nielsen, 2017). Resistance to insulin compromises insulin-driven glucose and lipid metabolism in insulin-sensitive organs such as the liver, adipose tissues, skeletal muscles, heart and kidneys, prompting local tissue and organ injury and pathogenesis of albuminuria and hypertension (Fu, et al., 2017; Rask Larsen, et al., 2018). In addition, hyperinsulinemia in insulin resistance contributes to metabolic dyslipidemia manifested as elevated triglycerides, small and dense low-density lipoprotein (LDL) particles and decreased HDL-c, leading to endothelial dysfunction, sympathetic nervous system hyperactivity and hypertension (Fu, et al., 2017). Insulin resistance occurs at multiple levels from the cell surface to the nucleus, including desensitization of the insulin receptor, downregulated insulin receptor substrate (IRS), suppression of PI3K and Akt signals, and lack of inhibition on Foxo1-activated gene transcription (Fu, et al., 2017). Onset of insulin resistance has multiple origins, although obesity and sedentary lifestyle along with unknown genetic factors interact seem to predominate (Templeman, Skovso, Page, Lim, & Johnson, 2017). A key pathological change associated with insulin resistance is elevated blood pressure. It is estimated that over 30% of hypertensive patients display features of cardiorenal metabolic syndrome (Seravalle & Grassi, 2016). In this context, insulin resistance stimulates RAAS to promote volume expansion and endothelial dysfunction. Functional and structural abnormalities in microvasculature such as endothelial dysfunction, poor capillary recruitment, low capillary density and microvascular remodeling may also contribute to insulin resistance in cardiorenal metabolic syndrome (Moreira, et al., 2015). Activation of PI-3 kinase by insulin stimulates nitric oxide synthase (NOS) although overt oxidative stress, particularly from O2, in cardiorenal metabolic syndrome converts NO to $ONOO^-$, resulting in protein damage, loss of NO bioavailability and impaired vasodilation in insulin resistance (Moreira, et al, 2015). To this end, patients usually receive targeted cardiorenal metabolic syndrome therapy only after insulin resistance/prediabetes or diabetes, hypertension and/or hyperlipidemia is confirmed (Rask Larsen, et al., 2018). Dietary and pharmacological manipulations to reduce insulin levels or restore insulin sensitivity are capable of eliciting weight loss and improve abnormalities associated with the cardiorenal metabolic syndrome (Rask Larsen, et al., 2018; Templeman, et al., 2017).

b. Obesity, abnormal fat distribution and adipose function

Obesity places a considerable burden on health care and the global economy, and contributes to the expansion of type 2 diabetes. Excess caloric intake and obesity, particularly visceral fat distribution, are critical to insulin resistance, diabetes, hypertension, dyslipidemia, and

reduced life expectancy (Aune, et al., 2016; Perrone-Filardi, et al, 2015). Obese individuals are usually abundant in dysfunctional adipose tissues, triggering metabolic dyslipidemia including elevated triglycerides, apolipoprotein B, LDL-c, low HDL-c, low-grade inflammation, hypertension, and elevated blood glucose (Maiano, Hue, Morin, & Moullec, 2016; Saltiel & Olefsky, 2017; Zylke & Bauchner, 2016). Dysfunctional adipose tissues prompt low-grade inflammation, program adipose expansion and visceral adiposity, skewing the immune system to a pro-inflammatory phenotype favor the development of insulin resistance and hypertension (Alberti et al, 2009; Saltiel & Olefsky, 2017). It is noteworthy that obesity may be associated with a paradox, as findings from epidemiological studies suggest there is improved survival and better prognosis for CVD and kidney disease outcomes in those who are overweight or obese (Lavie, McAuley, Church, Milani, & Blair, 2014). There is still a fair amount of controversy that exists regarding the mechanisms of the paradox as the survival advantage is lost in those with extreme obesity (Oga & Eseyin, 2016) and raises the issue whether the normal range of BMI should be redefined in those afflicted with chronic diseases (Egom, et al, 2017).

c. Neurohormonal dysrégulation

Neuroendocrine function is closely regulated by genetic background and external factors including psychosocial stress, food intake, use of alcohol and other drugs. Dysregulation of these complex neuroendocrine networks promotes the onset and development of metabolic disorders (Seravalle & Grassi, 2016). Increased activation of sympathetic nervous system manifested as increased spillover of norepinephrine is common in obesity (Seravalle & Grassi, 2016), as evidenced by the positive correlation between urinary norepinephrine metabolites and BMI. Altered neural or hormonal outflow contributes to derangements in substrate and energy metabolism. For example, sympathetic activation directly compromises insulin sensitivity while elevated circulating noradrenaline levels promote lipolysis in adipose tissues, but not in muscles. However, local administration of catecholamines induces muscle lipolysis. The lipolytic action of catecholamines is more pronounced in visceral adipocytes along with dampened antilipolytic effect of insulin, resulting in higher free fatty acid (FFA) release from visceral adipocytes (Menzies, et al., 2017). The autonomic innervations of fat tissue may also alter insulin sensitivity through adipose tissue hormones such as resistin and leptin, both with an essential role in metabolic regulation and adiposity (Perez-Perez, et al, 2017). Elevated plasma leptin levels may drive sympathetic activation and dampen insulin sensitivity in obesity (Seravalle & Grassi, 2016). Other components of cardiorenal metabolic syndrome may also contribute to increased sympathetic tone as evidenced by sympathetic activation with hypertension (Seravalle & Grassi, 2016; Tuomikoski & Savolainen-Peltonen, 2017). Not surprisingly, heightened sympathetic tone is responsible for a number of unfavorable cardiorenal metabolic responses (Mahu & Domingos, 2017; Seravalle & Grassi, 2016; Tuomikoski & Savolainen-Peltonen, 2017).

d. Aberrant gene expression and epigenetic disorder

Cardiorenal metabolic syndrome may be consequence of complex genetic and environmental (such as diet) interactions (Park, Kim, Lee, & Kim, 2017). A number of genes such as peroxisome proliferator-activated receptor (PPAR)-α, -ß and -γ are involved in the regulation of insulin sensitivity, adipogenesis, lipid metabolism and blood pressure.

Polymorphism in PPAR-α [Leu(162)Val, Val(227)Ala], PPAR-β/δ [+294T > C], or PPAR-γ [Pro(12)Ala and C1431T] can contribute to cardiorenal metabolic syndrome (Seravalle & Grassi, 2016). Moreover, levels of PPAR-γ gene were overtly elevated in oxidative stress (Hatami, et al, 2016). PPARs govern transcriptional regulation of uncoupling proteins (UCPs), members of the mitochondrial anion carrier superfamily regulating body temperature and energy balance (Castrejon-Tellez, et al., 2016). Genetic polymorphism of the promotor region (−866G/A) of UCP-2, is associated with higher prevalence of cardiorenal metabolic syndrome (Park, et al., 2017). UCP-2 gene has been shown to be significantly upregulated in the cardiorenal metabolic syndrome along with PPAR-α and PPAR-γ (Castrejon-Tellez, et al., 2016). Cardiorenal metabolic syndrome is also closely associated with genetic mutation of the adiponectin encoding gene ADIPOQ, which triggers decreased adiponectin levels, insulin resistance and hyperinsulinemia (Perez-Perez, et al, 2017). Recent data from our own group revealed that deficiency of adiponectin may predispose to the onset of obesity cardiomyopathy (R. Guo, Zhang, Turdi, & Ren, 2013) although adiponectin deficiency unexpectedly alleviated high fat diet-induced hepatic injury without affecting hepatic steatosis (R. Guo, Nair, Zhang, & Ren, 2017). Given the role of sympathetic activation in the cardiorenal metabolic syndrome, polymorphism of the ß-adrenergic receptor ADRB1 and ADRB3 genes (Arg389Gly and Trp64Arg) is deemed a susceptible gene for type 2 diabetes and lipid disorder (Burguete-Garcia, et al., 2014; Castrejon-Tellez, et al., 2016). Variant Arg389Gly of ADRB1 is associated with high LDL levels and the variant ADRB3 Trp64Arg is tied with increased levels of homeostatic model assessment-insulin resistance (HOMA-IR) and insulin (Burguete-Garcia, et al., 2014). Recent data have depicted a culprit role for the SLC35D3 gene located at or close to the D6S1009 site on the human chromosome 6 for obesity. Defective SLC35D3 gene disrupts delivery of dopamine in the central nervous system, prompting reduced exercise capacity, energy expenditure, metabolic control, and central obesity (Z. Zhang, et al., 2014). In fact, mutation of SLC35D3 gene occurs in 0.5% in obese population (Burguete-Garcia, et al., 2014). Moreover, exon sequencing in inheritable premature coronary disease, hypertension and diabetes revealed a high frequency of inheritable genetic mutation in Dyrk1B, a regulatory enzyme for muscle-adipose balance and blood glucose. Mutation of Dyrk1B disturbs blood glucose homeostasis (Z. Zhang, et al., 2014) and promotes metabolic syndrome (Keramati, et al, 2014). In addition to the list of genes mentioned above, genetic polymorphism of the lamin A/C (LMNA) (Ji, et al, 2016), insulin receptor substrate 1 (IRS1) (Kloting & Bluher, 2014), melanocortin receptor 4 (MC4R) (Ruiz-Ramirez, Lopez-Acosta, Barrios-Maya, & El-Hafidi, 2016), TCF7L2 (transcription factor 7-like 2) (Palizban, Rezaei, Khanahmad, & Fazilati, 2017), fat mass and obesity associated gene (FTO) (Elouej, et al, 2016; Rotter, et al., 2016) have also been documented to be associated with increased prevalence of cardiorenal metabolic syndrome.

In addition to the “metabolic susceptible genes”, dietary and environmental factors also play an essential role in the prevalence of cardiorenal metabolic syndrome (Gosadi, 2016; Park, et al, 2017). Dietary factor-dependent epigenetic modifications may regulate genome stability, the expression of mRNA and proteins to exert significant health effects (Ji, et al, 2016; Kunes, et al, 2015). Several epigenetic risk markers may be initiated or reversed by dietary and environmental factors such as the inverse correlation between méthylation of

suppressors of cytokine signaling-3 (SOCS-3) and the prevalence of metabolic disease (Hohn, Konig, & Jung, 2016). More importantly, the epigenetic DNA modifications (i.e. DNA méthylation, histone modifications) from dietary and environmental factors may predispose offspring to unfavorable metabolic changes in their early life (fetal and perinatal periods) and subsequent progeny for several generations, a phenomenon termed transgenerational inheritance (Smith & Ryckman, 2015).

e. Mitochondrial dysfunction, oxidative stress, inflammation and apoptosis

Ample evidence favors a key role for mitochondrial injury, oxidative stress, and apoptosis in cardiorenal metabolic syndrome (Bhatti, Bhatti, & Reddy, 2016). Mitochondria govern essential cellular function such as ATP production, reactive oxygen species (ROS) production and removal, intracellular Ca^{2+}regulation, and apoptosis (Bhatti, et al, 2016). ROS production occurs within and outside mitochondria through enzymatic and nonenzymatic machineries such as mitochondrial oxidative phosphorylation, nicotinamide adenine dinucleotide phosphate oxidases (NADPH oxidase or NOX), uncoupled NO synthase, xanthine oxidase, D-aminooxidase, p450 cytochromes, and proline hydroxylases. A major shift has been noted in the source of ROS with the progression of metabolic anomalies, from the early (NOX4-dependent), to the intermediate (NOX2-dependent) and late (mitochondria-dependent) stages (C. Y. Han, 2016). Oxidants including ROS and reactive nitrogen species (RNS) promote oxidation of lipids [lipid peroxidation - malondialdehyde, glyoxal, acrolein, and 4-hydroxy-nonenal (4-HNE)] and glucose (glycation - glyoxal and methyl glyoxal), resulting in reactive advanced glycation end-products (AGEs) and advanced lipid oxidation end-products (ALEs) to predispose the onset of cardiorenal metabolic syndrome. Elevated ROS production and dampened mitochondrial biogenesis as well as genes required for mitochondrial oxidative phosphorylation were reported in insulin resistance and type 2 diabetes (F. Dong, Li, Sreejayan, Nunn, & Ren, 2007). Therapeutic strategies to reduce mitochondrial and oxidative injury have been implicated in cardiorenal metabolic syndrome including lifestyle modifications (such as diet and exercise), pharmacological and mitochondria-targeted approaches (Bhatti, et al, 2016). Data from our laboratory revealed that the heavy metal scavenger metallothionein alleviates high fat diet intake and eNOS uncoupling-induced cardiac anomalies, mitochondrial injury, loss of mitochondrial DNA and mitochondrial biogenesis evidenced by peroxisome proliferator-activated receptor γ coactivator 1α (PGC-la) as well as the PGC-lα downstream nuclear factors (Ceylan-Isik, et al., 2009; F. Dong, ét al., 2007).

Inflammation, which initiates in adipose tissues eventually reaching circulation and other parts of body, perpetuates cardiorenal metabolic syndrome (Kloting & Bluher, 2014). Insulin resistance is one of the first consequences of sustained inflammation, since pro-inflammatory cytokines such as interleukins, and TNF-α abrogate insulin receptor phosphorylation and post-receptor action, leading to altered lipid storage, lipid spillover and dyslipidemia (Garbossa & Folli, 2017; Paniagua, 2016). Increased inflammatory infiltration also promotes oxidative stress and apoptosis to disturb metabolic homeostasis.

f. Impaired protein quality control and autophagy

Protein quality control mechanisms including UPS are essential to normal function of various cells, tissues, and organs through regulating synthesis, folding, trafficking, post-translational modification, assembly, disassembly, localization, and degradation of proteins (Parry & Willis, 2016). The occurrence of the pro-oxidative and proinflammatory states in cardiorenal metabolic syndrome, which include low-grade inflammation, oxidative stress, glycosylation, AGE formation, lipid peroxidation, protein oxidation, endoplasmic reticulum (ER) stress, and cytokine release, perturb the highly redox-sensitive UPS to compromise protein quality control, triggering proteotoxicity and cell injury (Hohn, et al., 2016). Proteases, including calpain, matrix metalloproteinase (MMP), cathepsin and caspase, serve as the major proteases governing the breakdown of proteins and participate in the pathogenesis of cardiorenal metabolic syndrome. MMPs and cathepsins alter metabolic processes via modification of extracellular matrix and intracellular proteins. On the other hand, calpain and caspases affect signaling cascade including activation of NF-κB and apoptosis (Hua & Nair, 2015). Proteases are gaining attention as biomarkers and therapeutic targets for metabolic diseases. Autophagy, another protein quality control mechanism to remove large injured or long-lived proteins or organelles, may be either up- or down-regulated in various metabolic diseases, exhibiting organ and tissue specificity (Andres, et al., 2016; Giricz, et at, 2017; Z. L. Li, et al., 2012; X. Xu, Hua, Nair, Zhang, & Ren, 2013; X. Xu & Ren, 2015). A reciprocal regulatory mechanism exists between lysosomal autophagy and key metabolic elements such as glucose and lipids (L. Liu, Liao, He, & Li, 2017; Ren & Taegtmeyer, 2015). For example, lipotoxicity in metabolic anomalies impairs lysosomal function and autophagy, further exacerbating lipid accumulation and ultimately cell injury (Taniguchi, et al., 2016). A more in-depth understanding of the role of autophagy in metabolic diseases should yield potential therapeutic strategies for better management of cardiorenal metabolic syndrome. Here, we will discuss dysrégulation and target therapy of autophagy in the pathogenesis and management of cardiorenal metabolic syndrome.

IV. Autophagy Regulation in Cardiorenal Metabolic Function (Short- and Long-term)

Autophagy plays a pivotal role in the maintenance of the body’s metabolism. Clinical and experimental evidence has depicted a link between autophagy and metabolic risk factors such as obesity, dyslipidemia, alcoholism, insulin resistance, hypertension, diabetes mellitus, sepsis, and inflammation (Choi, et al., 2013; Levine, Packer, & Codogno, 2015; H. Ma, et al., 2011; Sinha, et al., 2017; S. Wang & Ren, 2018; Y. Zhang, et al., 2018). Bioengineered models of autophagy also support an essential role for autophagy in systemic metabolic regulation. Global deletion of p62 promotes insulin resistance along with increased body fat mass (Rodriguez, et al., 2006). Heterozygous deletion of Atg7 (homozygous embryonic lethality) or Beclin 2 did not exhibit metabolic abnormalities although it accentuates ob/ob or high fat diet-induced insulin resistance, lipid accumulation and inflammation (Lim, et al., 2014). Atg5-deficient mice present poor removal of apoptotic bodies in development while inhibition of autophagy by Beclin-1 or Atg7 knockdown suppresses apoptosis (Burkewitz, et al., 2014), denoting a tie between autophagy and these biological processes. Monoallelic loss of Beclin 2, a newly identified member in the beclin family, triggers metabolic

derangement (increased food intake, body weight and insulin resistance), due to increased brain G protein-coupled receptor (GPCR) cannabinoid 1 receptor governing food intake and energy storage (C. He, et al., 2013). Interestingly, chromosome 1q43, the genetic locus that contains *beclin 2,* is associated with obesity and diabetes traits in human (Shmulewitz, et al., 2006). It is perceived that Beclin 2 regulates autophagy through binding to PI3K complex, or lysosomal degradation of GPCRs through an adaptor protein GASP1 (GPCR-associated sorting protein 1) (Rocchi & He, 2015). Fig. 4 summarizes autophagy derangement and accumulation of cytotoxic aggregates in response to metabolic stress.

Not only does change in autophagy affect metabolic homeostasis, however metabolic stress also affects autophagy status. Examples of altered autophagy in various individual components of cardiorenal metabolic syndrome are presented in Table 1. Autophagy is suppressed in genetic or diet-induced models of obesity in various tissues, including liver, skeletal muscle and cardiac muscle (E. Chang, et al., 2015; H. H. Chang, et al., 2017; C. He, et al., 2012; Hsu, et al., 2016; H. Liu, et al., 2017; X. Xu, Hua, et al., 2013; X. Xu & Ren, 2015; L. Yang, Li, Fu, Calay, & Hotamisligil, 2010). Elevated circulating insulin (an autophagy-inhibitory hormone) is believed be responsible for changes in autophagy genes, including Vps34, Atg12, Atg8, Atg5, Atg7 and Beclin 1 in hepatic cells from high fat diet or ob/ob mice, the effect of which can be reversed by Atg7 adenoviral transfection (Settembre, De Cegli, et al., 2013). A number of signalling pathways including FoxO1 are known to play a key role in the suppressed autophagy present in hyperinsulinemia (K. H. Kim & Lee, 2014; Sinha, et al., 2017). Given the pivotal role of mitochondria in metabolic homeostasis, mitophagy may serve as a mitochondrial clearance mechanism and a target for metabolic stress (Dorn, 2011; Pickles, Vigie, & Youle, 2018). Nix/BCL2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3L)-Atg8-LC3-II complex, phosphatase and PTEN-induced putative kinase 1 (PINK1) and the E3 ligase Parkinson protein-2 (Parkin) and FUN14 domain containing 1 (FundC1) serve as the main effective mitochondrial clearance machineries (Saito & Sadoshima, 2015). For example, phosphorylation of mitochondrial fusion 2 protein (Mfn2) by PINK recruits Parkin to mitochondria, resulting in the ubiquitination and degradation of Mfn2 activity (Saito & Sadoshima, 2015). Increased mitochondrial fission due to Mfn2 degradation is essential to packaging and digestion of autophagosome containing mitochondria. However, the role of mitophagy and other forms of selective autophagy in cardiorenal metabolic syndrome is less clear. We will discuss the regulatory role of autophagy first in cell metabolism, food intake and energy expenditure before dissecting the pathological role of dysregulated autophagy in individual component of the cardiorenal metabolic syndrome.

a. Autophagy in cell metabolism, food intake and energy expenditure

Autophagy is highly sensitive to changes in micronutrient environment and participates in the regulation of nutrient uptake, cell metabolism and recycling of essential nutrient components (Evans, et al., 2017; Kimmelman & White, 2017; Saxton & Sabatini, 2017). Growth factors, essential amino acids, lipid and glucose promote multiple cell signalling pathways pivotal for metabolic homeostasis, and the alteration of which directly regulates cellular autophagy status (Fig. 3). For example, starvation and reduced energy in the form of ATP/AMP are the best-characterized inducers for autophagy (Lapierre, et al., 2015). In cells

relying on glycolysis, glucose deprivation promotes autophagy through AMPK activation (Hardie, 2014). Interrupted glucose metabolism lowers the levels of ATP and certain precursor molecules for biosynthesis of nucleic acids and fatty acids. In metabolic stress with disturbed glucose metabolism, cells rely on mitochondrial oxidation of fatty acids and amino acids as the main energy source, at the expense of production of dangerous ROS species. These changes in lipid and glucose metabolism affect autophagy as deficiency in amino acid turns on autophagy reminiscent of growth factor withdrawal, leading to clearance of protein aggregates and damaged organelles, and recycling of nutrients to promote cell survival (Altman & Rathmell, 2012). The metabolic by-products including free fatty acids, ß-hydroxybutyrate and ammonia may also participate in the regulation of autophagy in the face of cardiorenal metabolic syndrome (Youm, et al, 2015).

Fatty Acids: Levels of fatty acids are heavily influenced by food intake and energy expenditure. Autophagy dysrégulation is common in dyslipidemia such as fatty liver disease (S. Yan, et al, 2017), suggesting a tie between autophagy and lipid disorders (M. Yang Zhang & Ren, 2018). Saturated and unsaturated fatty acids including palmitate and oleate stimulate autophagy, via distinct signaling mechanisms such as EIF2AK2 (or PKR) and MAPK8 (or JNK1) (Shen, et al, 2012). Stearoyl-CoA desaturase (SCD), which converts saturated lipids into monounsaturated lipids, promotes autophagy with a high content of unsaturated fatty acids in autophagy membranes (Paiardi, et al, 2017). SCD1 is required for early autophagosome formation and supplementation of oleate may rescue SCD1 inhibition-induced autophagic anomalies (Ogasawara, et al, 2014). The essential role of lipids in autophagosome formation also received support by the fact that patatin-like phospholipase-domain-containing 5 (PNPLA5) found in lipid droplets serves as autophagy initiation substrates, encompassing degradation of autophagic adaptors, bulk proteolysis, mitochondrial control and microbial clearance (Dupont, et al, 2014). Therefore, lipid droplets may induce autophagy despite being nutrients (Galluzzi, Pietrocola, Levine, & Kroemer, 2014; Khaldoun, et al, 2014). Autophagy induced by fatty acids may capture and deliver lipid droplets into lysosomes for degradation, representing a rather unique way to combat lipotoxicity in lipid derangement. For example, ω−3 fatty acids may provide protective effects against hepatic lipotoxicity through induction of autophagy (Y. Chen, Xu, Yan, Yu, & Li, 2015).

Amino acids: In the presence of amino acids (e.g, arginine, leucine, and glutamine), mTORC1 is activated by way of an amino acid sensor (e.g, a leucine sensor), amino acyl-tRNA synthetase (e.g, leucyl-tRNA synthetase). With amino acid shortage, mTORC1 is inhibited to promote ULK1 and autophagy. mTORC1 indirectly regulates autophagy through phosphorylation of transcription factor EB (TFEB), which governs lysosome- and autophagy-specific genes transcriptionally. With insufficiency of amino acids, at least five distinct, non-mutually exclusive mechanisms participate in the regulation of autophagy. First, loss of amino acids lead to the buildup of uncharged tRNA species, and activation of eukaryotic translation initiation factor 2α kinase 4 (eIF2AK4) and transcription factor 4 (ATF4) to facilitate autophagy (Galluzzi, et al, 2014). ATF4 is upregulated in response to microenvironmental stresses including amino acid depletion, oxidative and ER stress to favor autophagy (S. Song Tan, Miao, Li, & Zhang 2017). Second, amino acid shortage in

lysosomes facilitates the recruitment of mTORC1 to lysosomal surface and subsequently mTORC1 activation (Galluzzi, et al., 2014). Third, the loss of amino acids especially leucine, glutamate and glutamine suppresses intracellular acetyl-CoA (Galluzzi, et al., 2014), a central metabolite for global protein acetylation and autophagy (Webster, Scott, Traba, Han, & Sack, 2014). Forth, loss of amino acids can decrease the essential intermediate metabolite a-ketoglutarate to stimulate autophagy (Galluzzi, et al.,2014). Last but not least, loss of amino acids may turn on the AMPK-TSC2-mTORC1 cascade to promote autophagy. Findings in C. *elegans* and mammalian cells suggested that AMPK associates and phosphorylâtes ULK1 to engage autophagy in response to deprivation of multinutrient. It is noteworthy that the amino acid catabolic product ammonia may serve as a potent inducer of autophagy, in contrary to the inhib itory effect of autophagy induced by amino acids (Galluzzi, et al, 2014). Such ammonia-induced autophagy seems to be mediated via an AMPK-dependent and ULKl/ULK2/mTORC1-independent manner (Galluzzi, et al., 2014; Harder, Bunkenborg & Andersen, 2014). These amino acid-driven cellular mechanisms orchestra autophagic responses in the face of amino acid shortage.

Acetyl-CoA and NAD^+: As an essential metabolic intermediate denoting energetic state, acetyl-CoA affects enzymatic specificity, metabolism, mitosis (Pietrocola, Galluzzi, Bravo-San Pedro, Madeo, & Kroemer, 2015) and the balance between cellular catabolism and anabolism (Marino, et al, 2014). Pharmacological or genetic interventions to inhibit acetyl-CoA synthesis facilitate autophagy, while replenishment of acetyl-CoA suppresses starvation-induced autophagy (Marino, et al, 2014; Pietrocola, et al., 2015). Activation of acetyl-CoA-carboxylase leads to lipogenesis and obesogenesis (Sinha-Hikim, et al, 2017), coinciding with suppressed autophagy in fatty liver disease and obesity (Madrigal-Matute & Cuervo, 2016; S. Yan, et al, 2017). As the sole donor of acetyl groups for acetyl transferases, acetyl-CoA influences the acetylation profiles of several proteins including histones and regulates autophagy at the post-translational level via acetylation (Duran, et al, 2013; Pietrocola, et al, 2015). On the other hands, nutrient deprivation promotes buildup of NAD^+ (oxidized form) at the expense of NADH (reduced form), both essential substrates for metabolic circuitries such as glycolysis, the Krebs cycle, and oxidative phosphorylation. NAD^+ stimulates autophagy through histone deacetylases of the sirtuin family (Houtkooper, Pirinen, & Auwerx, 2012). Levels of relative (NAD^+/NADH ratio) and absolute NAD^+ may be regulated through inhibition of these enzymes or usage of precursors (e.g, nicotinamide, nicotinamide riboside), resulting in autophagy induction via the NAD^+-dependent sirtuins (Houtkooper, et al, 2012).

A thorough understanding of organismal homeostasis through balance between food intake and energy expenditure is essential to the development of strategies to combat cardiorenal metabolic diseases. Other than the classical metabolic regulation of glucose, fatty acid and other nutrients, autophagy also participates in the regulation of hematopoietic stem-cell and T cell metabolism to influence overall metabolic state. Autophagy protects hematopoietic stem cells against metabolic stress, which is pivotal to preserve the regenerative capacity of old hematopoietic stem cells (Ho, et al., 2017). Loss of autophagy in hematopoietic stem cells such as in aging and other disease states leads to build-ups of mitochondria and

metabolic stress, resulting in accelerated myeloid differentiation and impaired hematopoietic stem-cell renewal and regenerative ability.

b. Autophagy and insulin resistance

Insulin resistance is a cardinal feature of cardiorenal metabolic syndrome with physical inactivity, inflammation, type 2 diabetes mellitus, obesity, hypertension, and cardiovascular disease. Binding of insulin to its receptor stimulates the intrinsic tyrosine kinase activity of the receptor, and phosphorylâtes target proteins (insulin receptor substrates), to turn on two major kinases namely PI3K (metabolic) and MAPK (growth) (Muscogiuri, et al., 2017). Insulin resistance denotes loss of insulin sensitivity at the receptor or post-receptor levels leading to elevated plasma insulin levels (Muscogiuri, et al, 2017). Given the essential role of insulin as the major anabolic hormone in growth, development, glucose, fat, and protein metabolism, insulin resistance is believed to contribute to the early adverse cardiovascular and metabolic events in cardiorenal metabolic syndrome (Jia, Whaley-Connell, & Sowers, 2018; Ren & Anversa, 2015). Insulin resistance is shown to be distinctly governed by autophagy in insulin responsive tissues such as adipose tissues, skeletal muscles, pancreas, liver, and brain (James, O'Neill, & Nair, 2017; R. Singh, et al., 2009). Levels of insulin are controlled by crinophagy - a lysosomal degradation process of secretory granules. Crinophagy is stimulated at low glucose to promote degradation of insulin secretory granules, while the process is reversed at high glucose levels (Muscogiuri, et al., 2017). Crinophagy helps to maintain the balance between glucose and insulin production. On the other side of the coin, insulin levels and insulin sensitivity inhibit autophagy. Hyperinsulinemia may suppress autophagy, while dampened autophagy further inhibits insulin signaling, denoting a reciprocal regulation between the two (K. H. Kim & Lee, 2014; Sinha, et al., 2017). For example, although Atg7 haploinsufficiency does not exhibit metabolic defect, it promotes insulin resistance, lipid overload, and diabetes when crossed with ob/ob mice (Lim, et al., 2014). Findings from ob/ob mice revealed compromised autophagy in association with insulin resistance and ER stress, the effects of which were rescued by Atg7 (L. Yang, et al, 2010). As indicated in Table 1, compromised autophagy was also noted in livers, skeletal muscle and adipose tissues from diet- and dehydroepiandrosterone-induced insulin resistance (X. Li, et al., 2017; Qian, et al., 2018; X. Song et al., 2018). Insulin sensitization through pharmacological intervention or life style modification may improve insulin signaling and metabolic profiles in association with restored autophagy (H. Liu, et at, 2017; Wei, An, Jin, Li, & Xu, 2018; A. Xu & Sweeney, 2015). Although autophagy may protect ß-cell function (Marsh, et al, 2007), excessive autophagy leads to apoptosis and insulin resistance in cardiomyocytes and ß-cells in stress conditions (Fujitani, Ueno, & Watada, 2010; S. Li, H. Li, et al., 2017). It was indicated recently that inactivation of Vps34 PI 3-kinase, an integral autophagy initiating component, is capable of enhancing insulin sensitivity and metabolism through reprogramming of mitochondrial metabolism (Bilanges, et al., 2017). These findings collectively suggest a rather complicated role of autophagy in the regulation of insulin sensitivity.

c. Autophagy, diabetes mellitus and pancreatic defect

Diabetes mellitus is featured by hyperglycemia, oxidative stress and mitochondrial injury, all of which are under the tight regulation of autophagy (Barlow & Thomas, 2015; James, et al,

2017). Autophagy regulates normal function of pancreatic ß cells and insulin-target tissues, such as liver, skeletal muscle, and adipose tissue. With loss of autophagy homeostasis, damaged mitochondria accumulate, lead ing to an overt rise in ROS. Mice deficient in autophagy gene in ß-cells exhibited accumulation of damaged organelles, injured mitochondria, increases in ROS and reduction in glucose-stimulated insulin secretion (Ichimura, Kominami, Tanaka, & Komatsu, 2008; J. J. Wu, et al., 2009). The autophagy deficient mice were prone to the development of diabetes with marked ß-cell loss upon high fat diet challenge (Ebato, et al., 2008). In particular, pancreatic Atg7 knockout triggered impaired glucose tolerance, reduced insulin secretion, hyperglycemia and diabetes with normal or high fat diet intake (Ebato, et al., 2008) (H. S. Jung et al., 2008) or when cross-bred with ob/ob mice (Quan, et al., 2012). As stated above, pancreatic deficiency in Atg4b exhibited limited autophagic competence, robust increase in body weight in response to distinct metabolic challenges, reduced glucose tolerance and attenuated insulin responses. These mice are more vulnerable to experimentally induced diabetes. Interestingly, stimulation of autophagy by spermidine alleviated metabolic derangement (Fernandez, et al., 2017). These findings suggest that autophagy acts as an important protective mechanism for oxidative stress in insulin-target tissues and influences the resilience of the organism to develop diabetes. Likewise, altered autophagy has been implicated in the progression of diabetes through impaired ß-cell function and onset of insulin resistance (James, et al., 2017). Dysregulation of autophagy has been reported in animal models and human subjects of diabetes, likely due to lipid accumulation and inflammasome activation (Barlow & Thomas, 2015; J. Kim, Lim, & Lee, 2018). Although a causative role for ROS is confirmed in diabetes with proven benefit of antioxidants against diabetic complications in animal studies, clinical studies failed to consolidate the efficacy of antioxidant therapy, suggesting that antagonizing existing ROS by antioxidants may not be sufficient to reduce diabetic injury. Thus it is essential to develop a more effective therapeutic strategy for diabetic complications to eliminate defective mitochondria, which would otherwise generate ROS and release pro-death factors continuously. Enhanced autophagy may function as a unique protective mechanism against oxidative stress in diabetes, as novel anti-diabetic agents such as glucagon-like peptide-1 (GLP-1) agonist are shown to specifically target autophagy in diabetes (Arden, 2018). Other agents capable of enhancing autophagy such as imatinib and trehalose have also been shown to improve metabolic profile and ameliorate inflammation in diabetes with systematic autophagy insufficiency (Castillo, et al, 2013; J. Kim, et al., 2018; Lim, et al., 2014; Q. Xie, Lin, Li, & Chen, 2017). It is noteworthy that autophagy induction may also influence diabetes through its regulation of lipid accumulation in adipose tissues, liver and muscles to affect insulin resistance and pancreatic function (Barlow & Thomas, 2015; Sinha, et al, 2017).

d. Autophagy, obesogenesis, adiposity, adipose development and differentiation

Obesity is a global health issue attributed to the interplay between genetics and environment. Adipose tissues play a central role in obesogenesis in paracrine or endocrine fashion through pro-inflammatory adipokines including leptin, resistin, TNF-α and adiponectin (Mandviwala, Khalid, & Deswal, 2016). These adipokines elicit unfavourable metabolic responses such as cardiac depression, vascular reactivity, proteinuria, inflammation (e.g., interleukins and monocyte chemotactic protein 1) and coagulation (e.g., PAI), contributing

to cardiovascular dysfunctions (Mandviwala, et al, 2016). When energy supplies exceed the storage capacity of adipocytes under metabolic stress, adipocyte hyperplasia and hypertrophy occur. Adiposity or obesity promotes cardiovascular anomalies including cardiac remodeling, heart failure, hypertension and a spectrum of non-communicable diseases (Oga & Eseyin, 2016). The relative risk for a 10-cm rise in waist circumference and a 0.1-unit increase in waist-to-hip ratio are both 1.29 (Aune, et al., 2016). Recent evidence has depicted a rather important role for autophagy and lysosomal function in adiposity and organ complications (Jacob, et al., 2017; Sinha-Hikim, et al., 2017; Sinha, et al., 2017), coinciding with the close tie between autophagy and metabolic disorders (Maixner, et al., 2016). Genetic deletion of Atg7 presented increased lipid content when crossed with ob/ob mice (Lim, et al, 2014). Other studies noted the phenotype of adiposity, obesity and insulin resistance with deletion of Bec lin 2 and Atg4b (Fernandez, et al., 2017; C. He, et al., 2013). This is supported by the important regulatory role for autophagy in adipose tissue differentiation, or adipogenesis, which demands cytoplasmic reorganization in mitochondria (Jialal & Devaraj, 2018). Pharmacological inhibition of autophagy in human adipose tissue expiants promoted pro-inflammatory cytokine secretion (Maixner, et al., 2016). Along the same line, upregulation of autophagy in obese Wistar Ottawa Karlsburg W (RT1u) rats contributes to the regulation of visceral adipose tissue function and the balance between pro-inflammatory and protective adipokines (Kosacka, et al, 2018). These data indicate a retraining role for adipose autophagy in adipose tissue inflammation. Nonetheless, activated adipose autophagy contributes to pathogenesis of obesity complication, reminiscent of its role in chronic lung disease (Maixner, et al., 2016). Very recent evidence suggested that suppression of autophagy may induce brown-like adipocyte formation in adipocytes and adipose tissues, a process deemed beneficial for obesity treatment (Leu, et al., 2018). Intriguingly, siRNA-mediated Atg7 knockdown and pharmacological inhibition of autophagy in adipocytes or obese adipose tissues displayed beneficial effects in adiponectin secretion (Slutsky, et al., 2016). Thus, activated adipose autophagy noted in obesity might contribute to the endocrine defect of adipose tissue, linking obesity to its comorbidities. These observations are in line with the clinical findings that elevated adipose tissue autophagy is associated with a high-risk obesity phenotype (visceral fat, insulin resistance) (Maixner, et al., 2016). Recent evidence has supported a key role for transcriptional factors in autophagy-associated adiposity regulation. Transcriptional regulation of E2F1 in visceral (omental) adipose tissue are considered possible route for cardiorenal metabolic risks, including higher circulating free fatty acids, interleukin 6 (IL-6), insulin resistance, and low adiponectin levels. This association disappeared following adjustment to autophagy, indicating a compelling role for autophagy in adipose tissue E2F1-regulated cardiorenal metabolic morbidities. More importantly, E2F1-null adipocytes were less lipolytic, tended to respond better to insulin, secreted less leptin and more adiponectin, and, importantly, were more resilient to pro-inflammatory cytokines (Haim, et al., 2015). Transactivation of Atg4b by CCAAT/enhancer-binding protein ß (C/EBPß) was also reported to promote autophagy, leading to facilitated adipogenesis (L. Guo, et al., 2013).

The role of autophagy alterations in adipose tissue non-adipocyte cells is less clear. Bone marrow-derived macrophages from high fat-fed mice exhibited attenuated autophagy (K. Liu, et al, 2015) although its correlation with lipid handling remains unknown. Lysosomal

biogenesis was suggested to participate in lipid mobilization in adipose tissue macrophages in obesity (X. Xu, Grijalva, et al, 2013). In plaque, where macrophages accumulate lipid largely by engulfing modified LDL, autophagy may be required for reverse cholesterol transport (Ouimet, et al., 2011) and is therefore anti-atherogenic. This would be consistent with lipid droplet autophagy (lipophagy) as a mechanism for esterified lipid degradation (Rambold, Cohen, & Lippincott-Schwartz, 2015). The functional role of autophagy in adipose tissue macrophages, which accumulate lipids by either phagocytosis of adipocyte remnants or de novo lipogenesis, remains unclear. In addition, given the potential bidirectional links between autophagy and inflammation, it is intriguing to explore the cell-autonomous immune-metabolic contribution to adipose anomalies once defective autophagy is confirmed in obese adipose tissue immune cells. One of the most commonly considered dogma in immune cells is the link between attenuated autophagy and activated inflammation. It is intriguing to assess such concept in in adipose tissue immune cells or, conversely, that activated autophagy in adipose tissue cells acts to restrain “excessive” inflammatory response (Jansen, et al., 2012). Furthermore, it would be interesting to assess whether this involves transcriptional mechanisms and/or altered immune cell metabolism.

e. Autophagy and NAFLD (non-alcoholic fatty liver disease)

NAFLD is characterized by hepatic steatosis and is a manifestation associated with obesity, insulin resistance and cardiorenal metabolic syndrome, with no perceived cause for secondary hepatic fat accumulation such as alcohol intake, use of steatogenic medication, or hereditary disorders (De Meyer, et al., 2015; Shimano & Sato, 2017). Recent evidence has depicted a role for autophagy in the molecular mechanisms behind the etiology of NAFLD (Evans, et al., 2017; S. Li, X. Dou, et al., 2017; Sinha, Singh, & Yen, 2018). Deletion of autophagy genes, including Atg7, Vps34 and TFEB, exhibited increased hepatic lipid content, liver and body weight while overexpression of Atg7 improved hepatic insulin sensitivity (Jaber, et al, 2012; Settembre, De Cegli, et al., 2013; R. Singh, et al., 2009). Autophagy stimulates lipid metabolism and degradation of lipid stores (lipophagy), offering a new avenue for lipid degradation in addition to the classical cytosolic lipases (J. Liu & Debnath, 2016). This is evidenced by the beneficial effect of autophagy inducers on hepatic and circulating triglycerides or vice versa, lipid reducing agents such as ezetimibe with autophagy inducing properties (S. H. Kim, et al, 2017). The beneficial role for autophagy in NAFLD also received convincing support from the beneficial effect of thyroid hormones on hepatic lipid metabolism. Thyroid hormones are important regulators for lipid metabolism and promote fatty acid oxidation through hepatic autophagy (Mao, Yu, Wang, Guo, & Fan, 2016; Sinha, et al, 2018). The therapeutic promise autophagy is also implicated by its utility in other hepatic diseases including alcoholic liver disease, hepatocellular carcinoma, α1-antitrypsin deficiency, and viral hepatitis (Madrigal-Matute & Cuervo, 2016; Sinha, et al, 2018). Last but not least, it should be noted that controversy exists with regards to the precise role of autophagy in hepatic lipid metabolism and NAFLD, as improved lipid metabolism (reduced lipid content and improved insulin sensitivity) were also reported with hepatic deletion of autophagy genes including FIP200 and Atg7 (K. H. Kim, et al, 2013; D. Ma, et al, 2013; Shibata, et al, 2009). A number of scenarios may be responsible for the apparent discrepancies between autophagy and hepatic lipid metabolism including the

necessity for autophagy in lipid droplet formation and induction of protective mitokine (such as Fgf21) with deficiency of certain autophagy gene.

f. Autophagy and hypertension

Hypertension is an independent risk factor for cardiovascular and metabolic disease events (Go, et al,, 2014; Nwankwo, Yoon, Burt, & Gu, 2013). Most major guideline committees recommend that hypertension be defined as a systolic blood pressure is ≥ 140 mm Hg or diastolic blood pressure is ≥ 90 mmHg, or both, on repeated examination. Autophagy, as a catabolic mechanism, maintains endothelial cell alignment, vessel wall biology and atheroprotection, the dysrégulation of which may be a common mechanism for vascular injury and associated pathologies (Nussenzweig, Verma, & Finkel, 2015; Vion, et al, 2017). Evidence support that autophagic vacuoles are significantly reduced quickly after low-dosed isoproterenol administration (Pfeifer, Föhr, Wilhelm, & Dämmrich, 1987). Endothelial autophagy helps to limit atherosclerotic plaque formation by retarding apoptosis, senescence, and inflammation in endothelial cells (Vion, et al., 2017). Using genetically-engineered mice of TFEB, a master gene for autophagy and lysosome biogenesis, Fan and colleagues revealed that TFEB governs angiogenesis through activation of AMPKα and autophagy (Y. Fan, et al, 2018). More evidence has linked autophagy to a wider cascade of vascular processes including calcification of vessel wall, atherosclerosis and pulmonary hypertension (Nussenzweig, et al., 2015; Vion, et al., 2017). Furthermore, suppression of autophagy has also been observed pressure overload-induced cardiac dysfunction (Atsuko Nakai, et al., 2007). It is believed that a transitory suppression of autophagic activity may serve as an early contribution to the adaptive increase in myocardial workload. A recent genome-wide association (GWAS) study involving 5205 hypertensive patients and 5320 controls revealed a common variant in the damage-regulated autophagy modulator locus associated with hypertension (Larsson, et al., 2013). In general, autophagy is deemed to confer resistance against arterial or pulmonary hypertension (Lee, et al, 2011). Paradoxically, increased autophagy possibly via oxidative stress was believed to be responsible for pulmonary arterial hypertension-induced ventricular hypertrophy and diastolic heart failure (Rawat, et al., 2014). Currently, direct evidence for autophagy-regulated blood pressure is still lacking while a consensus seems to suggest a paracrine regulation of vasoactive substances in endothelium by autophagy. Further study is needed to discern the role for autophagy in vascular biology and blood pressure regulation, and the emerging strategies to target autophagy process for therapeutic benefit.

g. Autophagy and renal injury

Over nutrition and the development of obesity, insulin resistance with the compensatory hyperinsulinemia, elevations in systolic blood pressure with hypertension and dyslipidemia are metabolic disorders that also affect kidney function (Jia & Sowers, 2015; Kimura, Isaka, & Yoshimori, 2017; Sorop, et al, 2017; Whaley-Connell & Sowers, 2017). The mechanisms are complex but generally involve increases in intraglomerular pressure, hyperfiltration, and alterations in tubuloglomerular feedback, which are hemodynamic in origin, but also hypertrophic, proliferative, and inflammatory and oxidative pathways that govern extracellular matrix deposition and fibrosis formation. These cellular metabolic responses govern the onset and development of kidney disease. In this context, much of the work done

to investigate the metabolic origins of kidney disease have been done in experimental models of obese, insulin resistant, or diabetic rodents. Several studies in diabetic models have demonstrated that activation of mTOR as well as inaction of AMPK downregulate autophagy in the kidney and specifically in the proximal tubule which governs to a great extent the absorptive, lysosomal capacity of the kidney (Serra, et al., 2010). In this context, a recent group used a proximal tubule specific autophagy deficient mouse line with Atg5 gene deletion to reverse the effects of a high fat diet on proteinuria and kidney dysfunction (Yamahara, et al., 2013). Within this study, autophagy mediated the extent of injury through mTOR. In a similar autophagy deficient line, the loss of Atg5 mediated hypertrophy of the proximal tubule and fibrosis with accumulation of cytosolic amorphous material (Kimura, et al., 2011), these findings were augmented in response to ischemia-reperfusion injury and supported that autophagy regulates to a great extent proximal tubule function. Another line of evidence suggests that autophagy mediates to a great extent immune function in the kidney. In autophagy deficient cell lines, the calcineurin inhibitor cyclosporine mediates mitochondrial function, ROS formation and TGF-ß production (Kimura, et al., 2013; Serkova, Klawitter, & Niemann, 2003).

h. Autophagy, ischemia heart disease and cardiorenal metabolic syndrome-associated cardiac anomalies

Autophagy plays an essential role in the maintenance of cardiac geometry and function (Delbridge, Mellor, Taylor, & Gottlieb, 2017). Evidence of autophagy in human heart disease was first reported in patients with dilated cardiomyopathy (Shimomura, et al., 2001). A role for dysregulated autophagy was later confirmed in various heart diseases including ischemic and cardiorenal metabolic syndrome-related heart anomalies (Delbridge, et al., 2017). Analysis of autophagy gene fingerprint in human ischemia-reperfusion injury revealed elevated autophagic activity (increased LC3-I levels and LC3-II/LC3-I ratios) (K. K. Singh, et al., 2014). On the other hand, autophagy activity is reduced and lysosomal accumulation is increased in peripheral leukocytes of myocardial infarction patients (G. Wu, et al, 2011), denoting the complexity and tissue specificity in autophagy following ischemia-reperfusion injury. More studies revealed a double-edged sword for autophagy in myocardial ischemia-reperfusion injury. Data from our lab and others depicted a myocardial protective role for autophagy in ischemia phase. However, during reperfusion, autophagy is deemed detrimental and promotes excessive myocardial cell death (H. Ma, et al., 2011; Sciarretta, Maejima, Zablocki, & Sadoshima, 2018). Further data from our group depicted disparate roles of AMPK and Akt in the regulation of autophagy during ischemia and reperfusion phases, respectively (H. Ma, et al, 2011). These data suggested the therapeutic potential of autophagy in the management of ischemic heart diseases.

Onset and development of cardiac remodeling and contractile dysfunction are common in cardiorenal metabolic syndrome with data supporting a role for autophagy in the pathology of cardiac anomalies. Using an atherogenic diet-induced Ossabaw swine model of cardiorenal metabolic syndrome (obesity, dyslipidemia, and insulin resistance), increased cardiac output and lowered myocardial perfusion were noted with increased protein levels of Atg5 but decreased ULK1, Beclin1 and the LC3BII/I ratio (Z. L. Li, et al., 2012). In another study using high fat, high cholesterol diet-fed hypercholesterolemic swine, activated

upstream and downstream mTOR signaling, suppressed autophagy, and overt cardiac hypertrophy were noted, confirming a role of mTOR in cardiac autophagy dysrégulation (Glazer, Osipov, Clements, Sellke, & Bianchi, 2009). Using a 12-week 60% high fat diet feeding regimen, mice developed cardiorenal metabolic syndrome including obesity, hyperglycemia, hyperinsulinemia and dyslipidemia. Cardiac function was suppressed although autophagy was unaffected. Interestingly, a carbon monoxidereleasing molecule (CORM-3) promoted cardiac autophagy and improved cardiac function without affecting metabolic syndrome (Lancel, et al., 2012). Along the same line, caloric restriction improve myocardial autophagy and metabolic syndrome in mice fed 58% high fat diet for ten weeks, which prompted obesity insulin resistance and dyslipidemia (Cui, Yu, Wang, Gao, & Li, 2013). Data from our own group suggested that a 45% high fat diet intake for 20 weeks led to obesity, glucose intolerance, dyslipidemia, and insulin resistance. Heart function was compromised in these high fat diet-fed mice including reduced cardiac output and fractional shortening, cardiomyocyte contractile function and intracellular Ca^{2+} handling (X. Xu, Hua, et al., 2013). Our data further revealed apparently normal autophagy initiation along with suppressed autophagolysosome degradation (autophagy flux) in hearts from these fat diet-fed mice. In general, it is believed that abrogating autophagy defects by modulating autophagy signaling pathways or direct autophagy induction may help to rescue cardiac dysfunction in cardiorenal metabolic syndrome (F. Wang Jia, & Rodrigues, 2017). At this point, the precise role of autophagy is still controversial as different levels or even same levels of autophagy may exert distinct effects on the myocardium at a given disease stage. To this end, determining the precise role of autophagy in ischemia and cardiorenal metabolic disease-associated heart dysfunction should help to further understand disease pathogenesis and identify novel strategies for the optimal management of heart disease.

i. Autophagy and diabetic cardiomyopathy

Diabetic cardiomyopathy refers to a heart muscle disease independent of macro- and micro-vascular pathology, and contributes to the high risk of heart failure and high mortality in diabetic patients (Jia, Hill, & Sowers, 2018). Recent evidence has indicated altered autophagy in both type 1 and type 2 diabetic hearts. In particular, cardiac autophagy and autophagic flux were suppressed in type 1 diabetes mellitus such as streptozotocin and OVE26 mice, a genetic model of type 1 diabetes (Z. Xie, et al., 2011; X. Xu, Kobayashi, et al., 2013). Reduced levels of Atg12, the Atg12-Atg5 complex and AMPK activity may contribute to decreased autophagosome formation and autophagy in these typet diabetic models. Paradoxically, type 1 diabetes-induced cardiac injury was overtly attenuated in Beclin 1- and Atg16-deficient mice, and was exacerbated by beclin 1 overexpression in the same model of type 1 diabetes, favoring the notion of an adaptive response for decreased autophagy in type 1 diabetes (X. Xu, Kobayashi, et at., 2013). Given that autophagy favors this autoimmune process (Fierabracci, 2014), decreased autophagic activity in the pancreas might protect ß cells, to limit diabetes progression and cardiac damage.

Genetic ablation of Atg7 in pancreatic ß cells promoted islet degeneration, impaired glucose tolerance and insulin secretion (Ebato, et al., 2008; Fujitani, Ebato, Uchida, Kawamori, & Watada, 2009), denoting a role for autophagy in preserving normal cellular architecture and function. However, myocardial autophagic flux was reported to be increased in fructose diet-

induced type 2 diabetes, leading to pathologic remodeling of the heart (Mellor, Bell, Young, Ritchie, & Delbridge, 2011). This is consistent with the upregulation of autophagy in human type 2 diabetic pancreatic ß cells (Masini, et al., 2009). Munasinghe and colleagues recently showed that excessive autophagy may trigger loss of myocardial cells and compromised cardiac function (Munasinghe, et al., 2016). Nonetheless, cardiomyocytes isolated from db/db type 2 diabetic mice and high fat diet-induced obese mice displayed decreased autophagic activity (Sciarretta, et al., 2012). This is in line with the observation of decreased cardiac Atg5 albeit no change in LC3B) in a type 2 diabetic patient cohort (Montaigne, et al., 2014).

V. Intervention Targeting Autophagy for the Management of Cardiorenal Metabolic Diseases

a. Pharmacological intervention

The clinical guidelines for management of the cardiorenal metabolic syndrome target individual components of the syndrome to achieve cardiovascular benefits (Rask Larsen, et al., 2018). The main objective of cardiorenal metabolic therapy includes management of dyslipidemia, hypertension, glucose metabolism and obesity. Currently, the first-line pharmacological therapeutics for the cardiorenal metabolic syndrome are statins for dyslipidemia, renin-angiotensin-aldosterone system (RAAS) inhibitors for hypertension, metformin or sodium/glucose cotransporter 2 (SGLT) inhibitors or glucagon-like peptide 1 receptor agonists (GLP-1RAs) for glucose intolerance, and the GLP-1RA liraglutide for weight control (Rask Larsen, et al., 2018). Ample preclinical evidence has depicted the promises of autophagy modulators such as mTOR inhibitors, imatinib and trehalose in the management of various metabolic and cardiovascular diseases (Castillo, et al., 2013; Lim, et al., 2014; Q. Xie, et al., 2017; Y. Zhang, et al., 2018). Natural products from plants may also exert beneficial effect in metabolic tissues through enhancing autophagy (Fan, et al., 2017). As a key catabolic process for digestion and removal of cytoplasmic components, modulating autophagic activity, through targeting regulatory players in the core autophagy machinery, may affect disease processes (Y. Zhang et al., 2018). However, most of approved usage of autophagy modulators is for cancer therapy (Marinkovic, Sprung Buljubasic, & Novak, 2018). Targeting autophagy for the FDA approved drugs for cardiorenal metabolic syndrome remains merely associative at this stage. Several double-blind, placebo-controlled randomized trials mandated by the US Food and Drug Administration (FDA) examined cardiovascular safety of anti-diabetic and other metabolic agents in patients with type 2 diabetes. A role for autophagy induction has been indicated for the FDA-approved insulin sensitizer metformin in the management of pre-diabetes and diabetes (Jiang et at, 2014; Kalender, et at, 2010). Another class of insulin sensitizers, the PPAR-γ agonist thiazolidinediones, has also been shown to either stimulate (S. Yan, Yang Chen, Xi, & Jiang 2014) or suppress (H. Li, Zhang Yang & Wang 2017; Yao, Zheng & Zhang 2015) autophagy although the permissive role of autophagy regulation has not been validated for thiazolidinediones in metabolic diseases. More autophagy inducers such as rapamycin, trehalose and resveratrol may also benefit insulin resistance through improved insulin sensitivity, ß-cell fonction, and diabetic phenotypes, as indicated in Table 2 (Lim, et al., 2014; Rocchi & He, 2015).

Incretin-based therapies exhibit some promises in the treatment of cardiorenal metabolic diseases. Dipeptidyl peptidase-4 (DPP-4) inhibitors suppress the breakdown of GLP-1 and improve glucose and metabolic control in diabetic and/or obese patients (Scheen, 2018). Recent evidence suggested that DPP-4 inhibitors such as sitagliptin may exert its therapeutic effect against diabetic cardiovascular complications through augmenting autophagy in an AMPK-ULK1 dependent manner (Dai, et al., 2018; Murase, et at, 2015). DPP-4 inhibitor MK-626 was reported to restore insulin secretion via autophagy induction in high fat diet-induced mice (L. Liu, Liu, & Yu, 2016). It is noteworthy that the cardiovascular effects of DPP-4 inhibitors remain controversial with inconsistent findings in clinical trials (Fadini, et al., 2017; Verma, et at, 2017). DPP-4 inhibitors such as saxagliptin exhibit a poor cardiovascular profile with high prevalence of hospitalization for heart failure. Sitagliptin displayed little effect on the risk of heart failure although a recent randomized controlled trial Sitagliptin Preventive Study of Intima-Media Thickness Evaluation (SPIKE) suggested that sitagliptin retarded the progression of carotid intima-media thickness in diabetic patients compared with conventional treatment (Fadini, et al., 2017). More evidence has indicated a role for autophagy regulation in GLP-1-offered cardiorenal metabolic benefits. GLP-1 may exert beneficial effect on glucose and lipid homeostasis through autophagy-dependent mechanism in pancreatic ß-cells, hépatocytes and other cell types (Arden, 2018; Q. He, Sha, Sun, Zhang, & Dong, 2016). Interestingly, GLP-1 treatment was also reported to improve diabetic retinopathy through alleviation of autophagy in a GLP-1 receptor-ERK1/2-HDAC-dependent manner. Likewise, GLP-1 analogue was found to prevent obesity-associated glomerulopathy by inhibiting excessive autophagy in podocytes (H. Guo, et al., 2018). It should be noted the heterogeneity of GLP-l-offered cardiovascular benefit. For example, Liraglutide and semaglutide seem to lower the risk of composite cardiovascular outcomes whereas lixisenatide displays no reduction or increase in cardiovascular risk (Scheen, 2018). The SGLT2 inhibitor agents, are a new class of agents that reduces blood pressure, weight, visceral adiposity, hyperinsulinemia, albuminuria, and oxidative stress in patients with type 2 diabetes and metabolic diseases (Secrest, Udell, & Filion, 2017). In particular, SGLT2 inhibitors reduce body weight from 2.9 kg for monotherapy to 4.7 kg when used in combination with metformin. In the completed clinical trials to assess SGLT2 inhibitors, empagliflozin and canagliflozin displayed reduced risk of composite cardiovascular endpoints (Ford, et al., 2007; Secrest, et al., 2017). Recent findings from our own lab suggested that empagliflozin rescued myocardial microvascular injury in diabetes via AMPK-mediated inhibition of mitochondrial fission (Zhou, et al., 2018) although direct impact on mitophagy by SGLT-2 inhibitors remains to be explored.

Other therapies: Lipid lowering drugs, ß-adrenergic blockers and RAAS inhibitors have all been reported to offer beneficial effect against oxidative stress, inflammation, insulin resistance, and progression of cardiorenal metabolic outcomes. Statins, aspirins, ß-blockers, ACE inhibitors (ACEI), and angiotensin II receptor blockers (ARB) have all exhibited benefits on reducing the cardiovascular mortality due to proper risk management including myocardial infarction, stroke and hypertension (Rask Larsen, et al., 2018). It was estimated that 44% of the decrease in cardiovascular mortality between 1980 and 2000 was due to risk factor modification with 24% attributable to reduction in cholesterol and 20% attributable to reduction in blood pressure (Ford, et al., 2007). Although autophagy regulation is not

considered the main mechanism of action for any of these agents, the ability to modulate autophagy may have contributed to the beneficial action of these pharmacological agents in the maintenance of cellular homeostasis and cardiorenal metabolic function. For example, oral or stent-based delivery of the autophagy inducers such as rapamycin, rapalogs or everolimus possess pleiotropic anti-atherosclerotic effects through control or retardation of atherosclerotic growth and destabilization of atherosclerotic plaques (Martinet, De Loof, & De Meyer, 2014). It was also suggested that ACEI or ARB rescued impaired autophagy in high glucose-induced endothelial apoptosis (F. Chen, et al., 2014). It is of note that regulation on autophagy may only provide add-on benefit for these agents in the management of cardiorenal metabolic anomalies beyond their well-characterized mechanism of action. Most recent studies reported a role for micro RNAs in cardiorenal metabolic diseases. For example, miR199a-5p was reported to suppress hepatic insulin sensitivity via inhibition of Atgl4-mediated autophagy (B. Li, et al., 2018). Dubinsky and colleagues identified let-7 miRNAas an amino acid sensor to prevent mTORCl activation and trigger autophagy (Dubinsky, et al., 2014). More evidence also suggested increased levels of miRNA-9 and miRNA-124a in obese subjects and overexpression of these micro RNAs confers lipid accumulation in adipose tissues (Mentzel et al., 2015). Thus, identification of the roles of the different miRNAs may provide novel therapeutic targets for prevention of metabolic diseases in future.

b. Life style modification, exercise, cessation of smoking.

Although available information is still controversial with regards to the role of autophagy in the pathogenesis of metabolic diseases, autophagy regulation is increasingly appreciated for the control of metabolic and cardiovascular homeostasis (R. Guo, et al., 2013; Maixner, et al., 2016). However, inconsistent data were using various animal species and strain with regards to the role of autophagy in cardiorenal metabolic syndrome. In particular, effective and specific pharmacological regulators for autophagy still remain somewhat limited, making it pertinent to search for potent non-pharmacological measures to regulate autophagy. Indeed, the changes in autophagy in cardiorenal metabolic syndrome were found to be heavily influenced by many factors, including age, gender, and life style factors. Ample evidence has suggested that caloric restriction, weight loss, regular physical exercise and smoking cessation can positively modify metabolic abnormalities, improve systemic and tissue insulin sensitivity, and lessen the progression of CVD (Ryter, Koo, & Choi, 2014). The Diabetes Prevention Program regimen showed that therapeutic lifestyle changes (TLCs) such as dietary modifications and physical activity had a far better impact than pharmacological options. For example, exercise as part of lifestyle intervention can prevent impairment of cardiac function and increase LV ejection fraction by 2% to 5% in patients with obesity and type 2 diabetes (Jia, Jia, & Sowers, 2016). In a recent clinical trial involving 100 obese older patients with stable heart failure and preserved ejection fraction, caloric restriction diet and aerobic exercise training, both known facilitators of autophagy, were reported to enhance peak oxygen consumption, and the effects may be additive (Kitzman, et al., 2016). Physical exercise is deemed a physiological stimulus for metabolic adaptations to benefit human health. Although the beneficial responses of exercise were traditionally credited to the biosynthesis of metabolic proteins and organelles, recycling of cellular components by autophagy has recently emerged as a unique mechanism in the

adaptive responses to exercise (Halling & Pilegaard, 2017). Exercise may turn on BCL2-mediated autophagy, thus contributing to the beneficial metabolic effects of exercise against high fat diet intake (C. He, et al., 2012). It is perceived that a biphasic autophagy response may be mobilized during exercise, resulting in both an acute induction and a long-term potentiation of autophagy. A number of transcriptional paradigm have been indicated in exercise-facilitated autophagy responses including Forkhead box O (Foxo), TFEB, p53 and PGC-1α, to fuel sustained autophagic activity (Vainshtein & Hood, 2016). More recent study indicated that aerobic exercise training improves the quality of life, cardiorespiratory fitness, and cardiorenal metabolic profile in overweight/obese women with polycystic ovary syndrome (PCOS) (Brennan, et al., 2017; Costa, et al., 2018). PCOS is associated with excess weight gain and multiple pregnancy complications, including preeclampsia, gestational diabetes, and large babies, due to hypothalamic-pituitary-ovarian (HPO) defect-induced endocrine abnormalities (e.g., hyperandrogenism and hyperinsulinemia) (Bani Mohammad & Majdi Seghinsara, 2017). Both elevated (D. Li, et al., 2018) and suppressed (Su, et al., 2017) autophagy were noted in PCOS depending on models or timing of PCOS development. Although direct evidence for autophagy in lifestyle modification (control of weight gain)-offered first-line treatment for PCOS (Brennan, et al., 2017) is still lacking, exercise-associated cellular machineries such as activation of AMPK and autophagy have been confirmed to rescue against disrupted implantation process in PCOS due to uterine defects (Y. Zhang, et al., 2017). These findings suggest potential therapeutic usefulness of metformin and autophagy in PCOS patients with uterine defect. More in depth work is needed to consolidate the precise interplay between physical exercise and autophagy in metabolic disorders such as PCOS. More evidence also depicted a role for autophagy in cigarette smoking-induced chronic anomalies (G. Wang, et al., 2017), denoting the therapeutic promises of targeting autophagy in smoking-induced chronic diseases such as pulmonary diseases although further study is needed for metabolic disorders. Perhaps more intriguingly, physical activity, but not dietary intake, alleviates the FTO polymorphism-induced metabolic anomalies in humans (Petkeviciene, et al., 2016), suggesting a gene-environment interaction. Thus, a better understanding of the role for autophagy in life style modification-induced benefit against metabolic disorders should shed some lights towards a better management of the cardiorenal metabolic syndrome. It is noteworthy that bariatric surgery is also regarded as one of the most effective strategies to control obesity and CVD since bariatric surgery can reduce body fat and offer beneficial effects on maintaining normal adipocyte and adipose tissue function lessening dyslipidemia, insulin resistance, dysglycemic hypertension, and associated CVD (Jia, et al., 2016).

c. Epigenetic modulation

Autophagy is primarily a cytoplasmic event to remove damaged and long-lived materials in stressed conditions. However, recent evidence has depicted occurrence of transcriptional and epigenetic regulation of autophagy within the nucleus (Baek & Kim, 2017; Fullgrabe, Klionsky, & Joseph, 2014). Epigenetic DNA modifications [chromatin remodeling, DNA méthylation (at the 5’-position of cytosine residues within CpG dinucleotides), histone modifications (acetylation, méthylation, phosphorylation, ubiquitination, sumoylation) and small noncoding RNA] develop in response to environmental factors to promote phenotypic changes of metabolic traits (Kunes, et al., 2015). These gene-environment interplays

converge at the metabolic-epigenome-genome axis to determine the metabolic traits. Although the overall risk of metabolic diseases can be largely attributed to poor-/over-nutrition, unhealthy life style, drinking and smoking in adult life, evidence has suggested that predisposition of metabolic anomalies start early in life, such as in fetal and perinatal periods through modifiable epigenetic changes (Smith & Ryckman, 2015). These metabolic changes (e.g., the “thrifty phenotype”) are visible not only in individuals exposed to environmental factors but also in subsequent progeny for multiple generations, a phenomenon termed as transgenerational inheritance. In particular, maternal undernutrition or overnutrition affects covalent modifications of fetal genome and its associated histones that are carried forward to subsequent generations for risk of cardiorenal metabolic syndrome. To this end, a better understanding of the epigenetic cues for various metabolic derangements should be critical for phenotypic change in adulthood and prevention of cardiorenal metabolic syndrome (Kunes, et al., 2015). Several tightly controlled transcriptional factors (e.g., TFEB and ZKSCAN3), and histone modifications [CARM1 H3R17 methyltransferase, acetylated Lys16 of histone 4 (H4K16ac), SIRT1 H4K16 deacetylase, hMOF H4K16 acetyltransferase, EZH2 H3K27 methyltransferase and dimethylated H3K9 (H3K9me2)] have been associated with autophagy and may provide short-term transcriptional and potential long-term regulation on autophagy and cell fate (Fullgrabe, et al., 2014). Moreover, amino acids (e.g., glycine, histidine, and methionine) and vitamins (B6, B12 and folate), with a known regulatory role on autophagy, provide methyl donors for DNA and protein méthylation. Intervention targeting epigenetically disturbed metabolic pathways via dietary supplementation with nutrients (functional amino acids and vitamins) has been shown to affect one-carbon-unit metabolism, gene expression, as well as protein méthylation and acetylation, resulting in improved health and well-being of affected offspring (Jia, et at, 2016). Nonetheless, whether autophagy regulation contributes to the beneficial effect of dietary nutrients remains elusive at this time. Food nutrients and metabolic supply-demand dynamics constitute environmental factors that interact with our genome influencing health and disease states.

While acute and rapid response of autophagy typically happens in the cytoplasm, prolonged starvation leads to transcriptional activation and epigenetic changes such as histone modification in the control of autophagy and cell fate. Recent evidence has depicted a tie between histone H3R17 dimethylation and autophagy (Shin, Kim, Kim, & Baek, 2016). Glucose starvation increases H3R17 dimethylation resulting from coactivator-associated arginine methyltransferase 1 (CARM1) induction in the nucleus. It is perceived that CARM1 serves as a coactivator of TFEB for activation of autophagy and lysosomal genes. Linder glucose-rich state, nuclear C ARM1 is degraded by the ubiquitin-dependent SKP2-SCF E3 ubiquitin ligase. When glucose starvation persists, AMPK gets accumulated in the nucleus to promote downregulation of SKP2 in the nucleus thus allowing CARM1 to escape from SCF E3 ubiquitin ligase, resulting in the transcription of various autophagy-related genes (H. J. Shin, et al., 2016). The role for H3R17 dimethylation in autophagy received consolidation from the autophagy suppressing property in compounds (e.g., ellagic acid) that block H3R17 méthylation (H. R. Shin, et al., 2016). These kinds of histone modifications in the nucleus seem to be a prototype of protein stabilization in certain cellular compartments during starvation-induced autophagy (Baek & Kim, 2017). Acetylation (such as in H4K16) has also

emerged as an integral regulatory part for autophagy. The genome-wide investigation suggested that rapamycin promotes H4K16 deacetylation (coinciding with downregulation of hMOF without changing Sirt1 levels or activity) and associated transcriptional activation of autophagy-related genes (Baek & Kim, 2017; Fullgrabe, et al., 2014). The importance of acetylation in autophagy regulation also received support by the role of acetyl-CoA (as the sole acetyl-group donor for protein acetylation) in epigenomics and metabolism. In the setting of metabolic disorder, the mitochondrial network is essential to the metabolic-epigenome-genome regulation of various metabolites (NAD^+, acetyl CoA, ATP) serving as substrates/cofactors for acetyl transferases and deacetylases (e.g. sirtuins) (Aon, Cortassa, Juhaszova, & Sollott, 2016). The nucleo-cytosolic acetyl-CoA functions as a phylogenetically conserved inhibitor of starvation-induced and aging-associated autophagy, and therefore serves as a metabolic rheostat, connecting metabolic state to autophagy regulation through protein acetylation. This notion receives support from the inverse relationship between acetylation of histones/cytosolic proteins and autophagy (Schroeder, et al., 2014). More evidence suggests that acetyl-CoA-suppressed autophagy involves regulation of histone acetylation and changes in autophagy-relevant transcriptome (Eisenberg, et al., 2014). Understanding of DNA méthylation and histone modification landscape in autophagy-related metabolic diseases should be a promising area for study of disease pathogenesis and drug development for metabolic control.

VI. Future Perspectives and Challenge in Autophagy Drug Development

A tremendous effort has been engaged towards the management of the cardiorenal metabolic syndrome although the advance in new drugs and procedures still face many problems and challenges. Perhaps genetics, epigenetics and precision medicine will unlock some of the mysteries of cardiorenal metabolic syndrome and the metabolic anomalies that underlie the cardiovascular sequelae, but this will take time and more immediate solutions are needed. Recent intensive attempts in the pharmacological modulation of autophagy have offered new avenues in the management of cardiorenal metabolic syndrome and metabolic derangement (Cheng, et al., 2013 ; Maixner, et al., 2016). A common denominator in the onset and development of cardiorenal metabolic syndrome and associated metabolic derangement is the maintenance of metabolism, adiposity, proteostasis, and organelle function (Cheng, et al., 2013; Maixner, et al., 2016). Ample evidence denotes a pivotal role for autophagy as a major mechanism to maintain metabolic homeostasis (Maixner, et al., 2016). As such, a number of autophagy-targeting compounds have been developed and approved for use in humans (Table 2), although some of these agents are still suboptimal for clinical practice. Currently, induction of autophagy and autophagic flux is predominantly dependent on nutrient sensors such as mTORand AMPK, and the insulin-IGF1 cascade. Autophagy modulators may be classified into mTOR-dependent and -independent. mTOR and AMPK regulate autophagy via direct phosphorylation of their downstream proteins. It is believed that hyperactivation of mTOR may serve as a main contributor for metabolic derangement by suppressing autophagy. For example, activation of skeletal muscle MTORC1 may result in autophagy inhibition and myopathy (Castets, et al., 2013). Thus nutrient signaling via mTOR provides a central mechanism and a possible drug target for intervention of autophagy- and lysosomal-related anomalies including adiposity (Settembre, Fraldi, Medina,

& Ballabio, 2013). Recent evidence has depicted a pivotal role for mTOR phosphorylation of TFEB at the lysosomal membrane for autophagy flux regulation (Martina, Chen, Gucek, & Puertollano, 2012). More evidence has suggested the contribution to sustained transcriptional regulation of autophagy (Fleming Noda, Yoshimori, & Rubinsztein, 2011).

One other added benefit in targeting autophagy for pharmacotherapy may be related to the development of cell resistance to antineoplastic therapies. In these situations, interference with autophagic response (in combination of chemotherapy) should represent a good therapeutic strategy to enhance the effects of chemotherapy and improve the clinical outcomes, given that autophagy inhibits chemotherapy-induced apoptosis (Aveic & Tonini, 2016).

VII. Summary and Conclusion

In conclusion, cardiorenal metabolic syndrome is of growing relevance for public health, not only in general population but also in subpopulations that are more prone to the syndrome (Hemkens & Bucher, 2014). Accumulating evidence has emphasized a major role for autophagy in adiposity and metabolic regulation. Both transcriptional and epigenetic regulatory pathways can offer key information in the disease pathogenesis and provide attractive entry points for drug development in an effort to manipulate autophagy activity. Alternatively, non-pharmacological approaches such as life style modification (e.g., exercise and diet control) may also contribute to autophagy induction and benefit organismal health (Lapierre, et al., 2015). Nonetheless, successful development of therapeutic autophagy agents requires a much thorough understanding of metabolic profiling in the pathogenesis but also the regulatory networks of transcriptional factors, epigene tic modulations, their potential interactions among each other or with other factors (Cheng et al., 2013).

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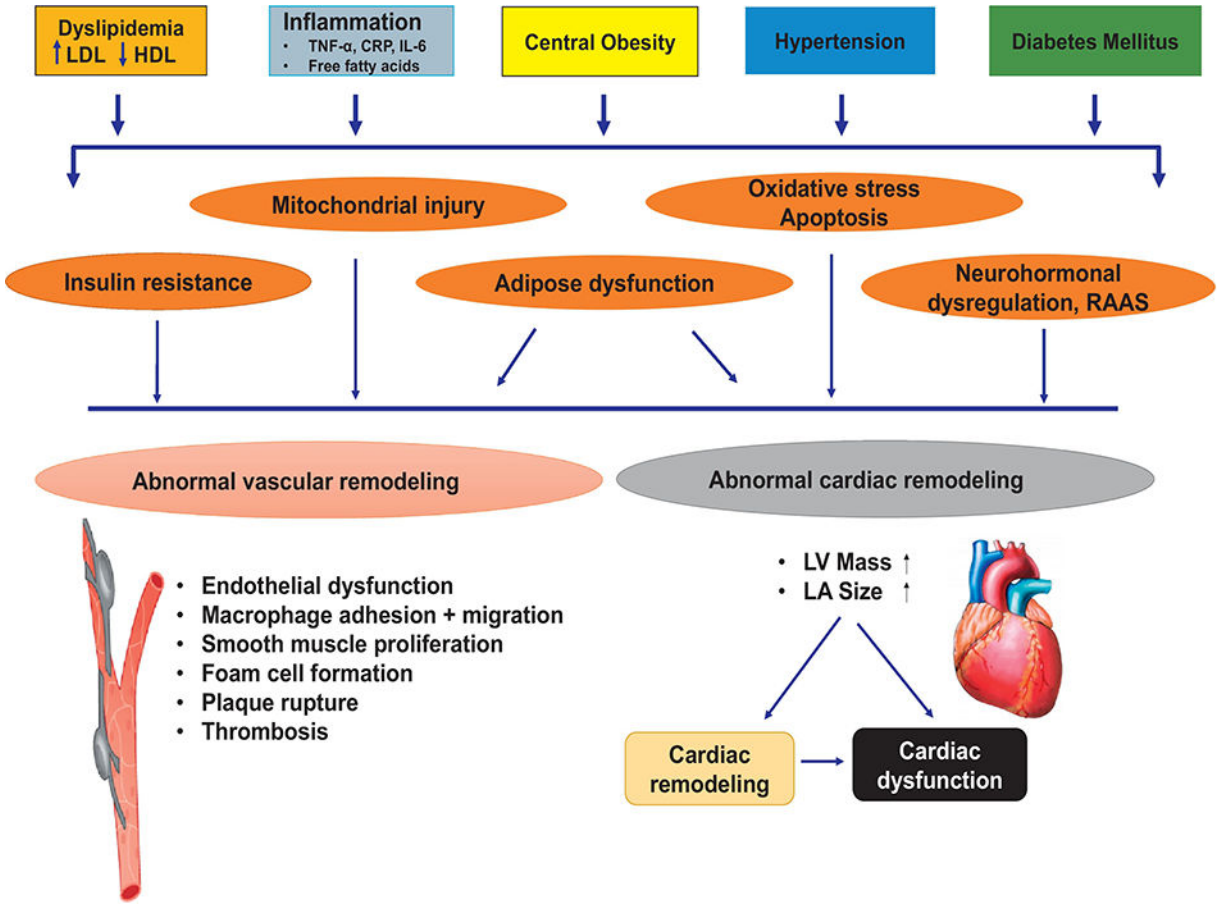

Figure 1:

Schematic diagram displaying various contributing factors for cardiorenal metabolic syndrome in the complex pathophysiology of cardiovascular complications. RAAS: renin angiotensin aldosterone system; CRP: C reactive peptide; TNF-α: tumor necrosis factor α; IL-6: interleukin 6 [adapted from (Y. Zhang & Ren, 2016) with modifications].

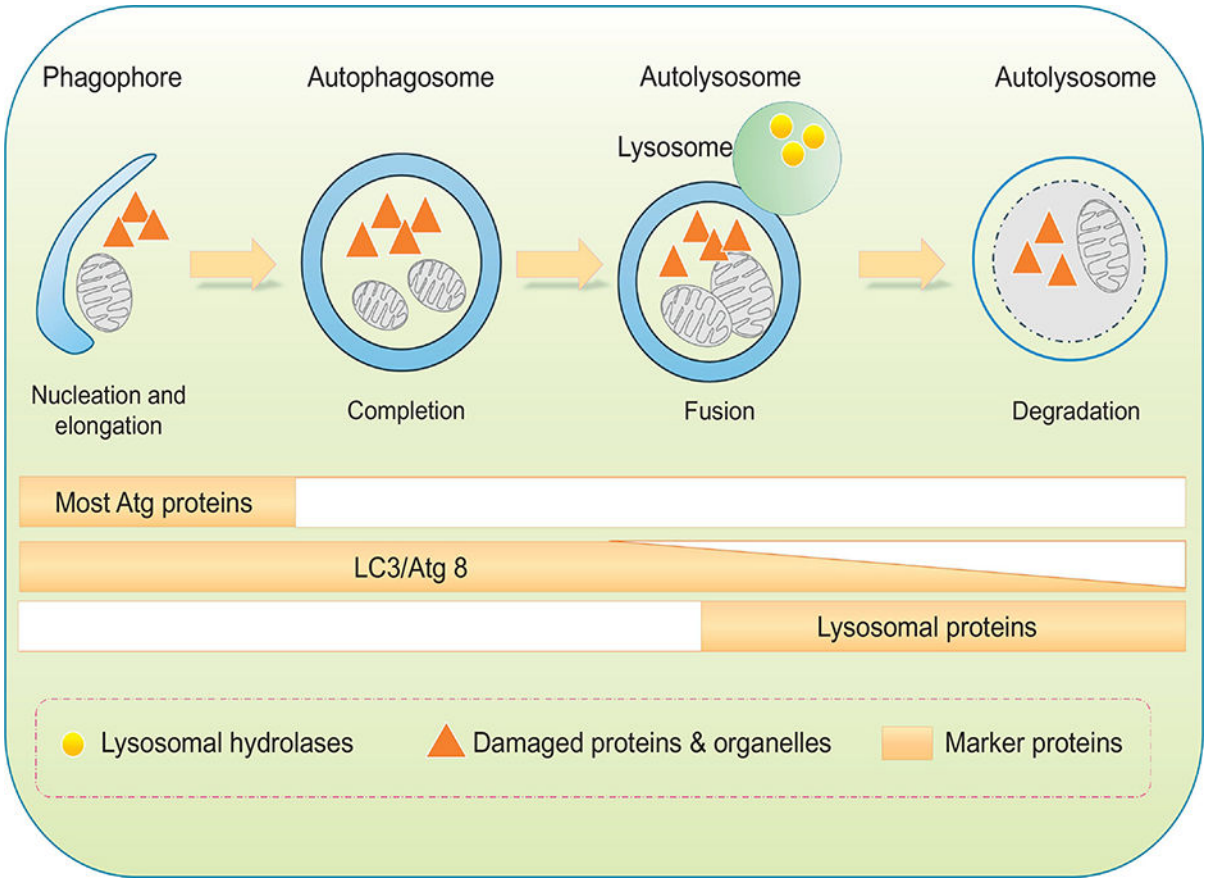

Figure 2:

Schematic diagram of sequential autophagy events in a step-wise manner. Phagophore forms with initial sequestration of aged or damaged proteins and organelles; phagophores then undergo a series of further membrane expansion and elongation events to yie ld a completed double-membrane sequestering vesicle named autophagosome. During formation of autophagosome, various substrates (cytosolic proteins, lipids, nucleic acids, glycogen, damaged organelles, and invasive microbes, also known as cargo) of autophagy are encapsulated within the autophagosomal vesicle. Autophagosomes fuse with lysosomes to form autophagolysosmes, where cargos are digested by lysosomal hydrolases. Protein markers are identified throughout each individual steps. Most ATG proteins are visible during early stages of autophagy initiation while the elevated levels of lipidated LC3/Atg8 can sustain for a much longer period of time.

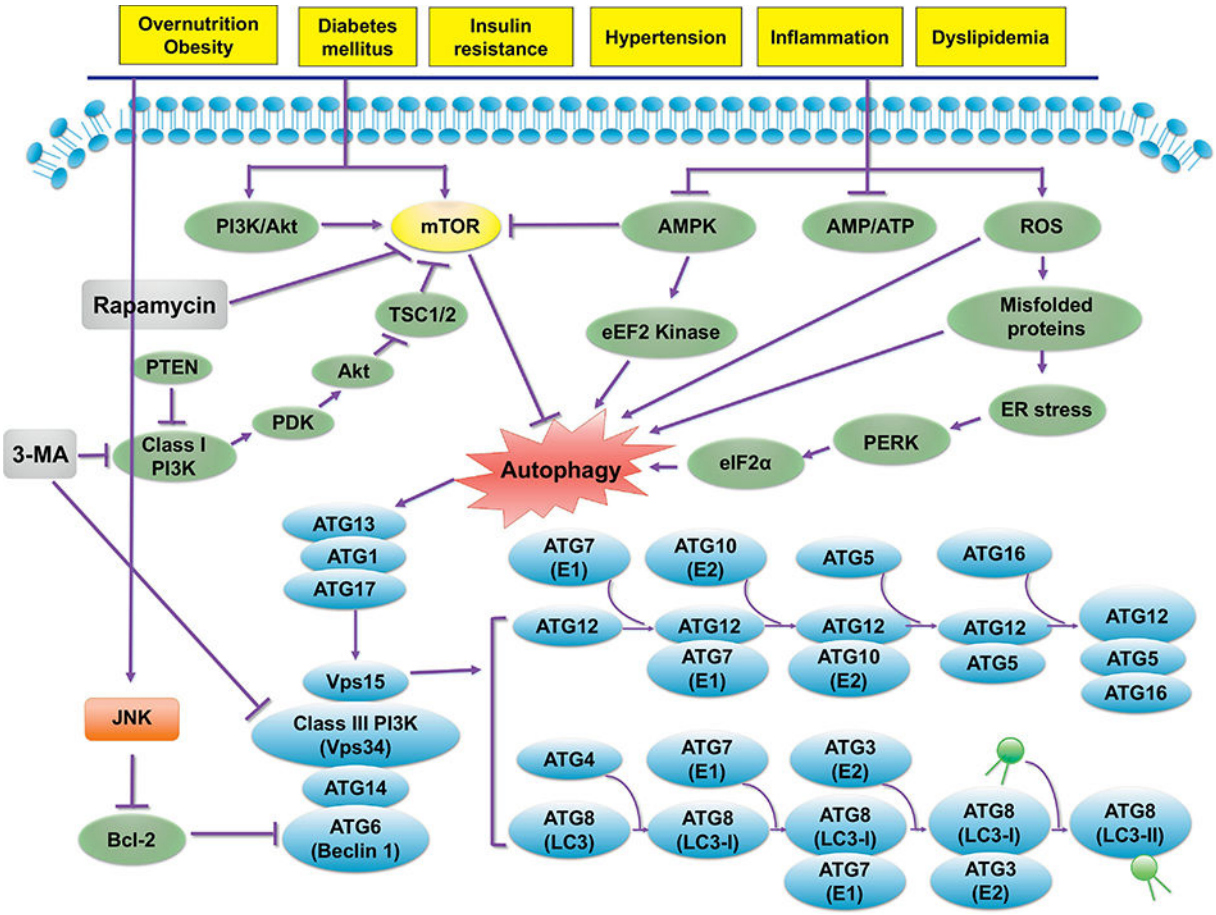

Figure 3:

Autophagy regulatory mechanisms in response to various cardiorenal metabolic stimuli (e.g., overnutrition/obesity, hyperlipidemia, insulin resistance, diabetes mellitus, inflammation and hypertension). The PI3K-Akt and AMPK signaling cascades represent the two major cell signaling pathways in response to cardiorenal metabolic stress. Typically, mTOR (with PI3K-Akt being the upstream activator) suppresses autophagy through inhibition of the ULK1 complex (ULK1-ATG13-FIP200) that is required for autophagy induction. AMPK activates the ULK1 complex or indirectly suppress mTOR to initiate autophagy. ROS directly or indirectly (through ER stress) turns on autophagy. The mTOR-independent autophagy regulating autophagy are less clear. One example is c-Jun N-terminal kinase (JNK)-regulated phosphphorylation (or inhibition) of Bcl-2, leading to relieve of Bcl-2-Beclin 1 coupling and its inhibition on autophagy induction. The ULK1 complex consisting of ATG1 (ULK1)-ATG13 and ATG17 recruits Vps34, Beclin-1, and Vpsl5 for autophagosome synthesis, possibly through mTOR-independent pathway(s). Two ubiquitin-like conjugation systems involving ATGs govern the elongation of phagophores. The ATG5-ATG12 conjugation involves ATG7 (El-like) and ATG10 (E2-like), whereas the light chain 3 (LC3, also commonly known as ATG8)-LC3-I- phosphatidylethanolamine (PE) conjugation involves ATG4 (a cysteine protease), ATG7 (El-like), and ATG3 (E2-like). The ATG5-ATG12 conjugate generates a complex with ATG16 to control LC3-I-PE conjugation (resulting in LC3-II). Arrowheads and “T” ended line lines represent activation and

inhibition, respectively. AMPK, AMP-activated protein kinase; Akt: also known as Protein Kinase B (PKB); mTOR, mammalian target of rapamycin; Rheb, Ras homology enriched in brain; TSC, tuberous sclerosis complex. Part of this cartoon is modified from (Y. Zhang, et al., 2018).

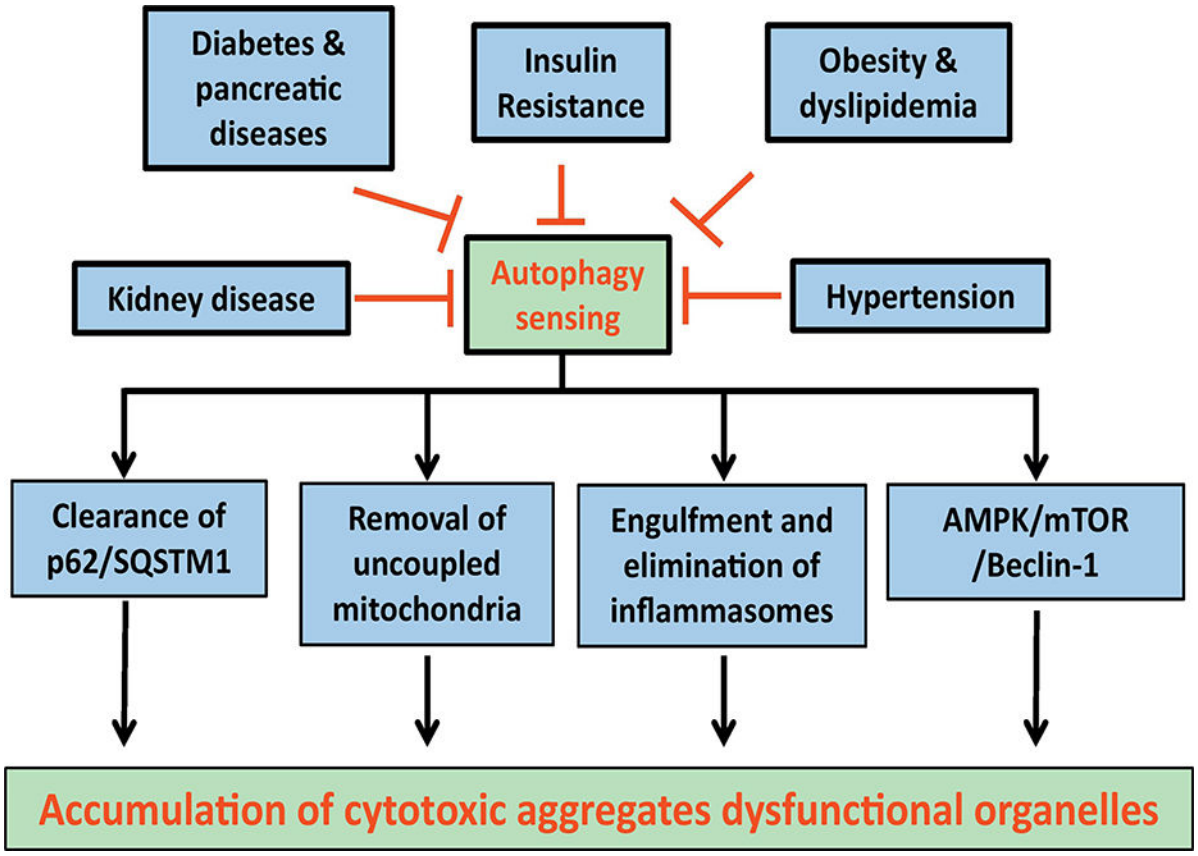

Figure 4:

Various components of the cardiorenal metabolic syndrome may compromise autophagy sensing mechanisms leading to compromised autophagy regulatory machineries such as lysosomal degradation, selective removal of mitochondria and other organelles, engulfment of inflammasome and a number of cell signalling molecules governing autophagy, leading to accumulation of cytotoxic aggregates and dysfunctional organelles.

Table 1:

Examples of autophagy change in individual compoments of the cardiorenal metabolic syndrome

Change of Autophagy in Insulin Resistance, Diabetes Mellitus and Pancreatic Defect			
Model and Organ	**Autophagy**	**Autophagy parameters**	**Reference**
Dehydroepiandrosterone-indued insulin resistance; Skeletal muslces	Suppressed	Activated mTOR, decreased LC3- II/LC3-I, and increased p62	X. Song, et al., 2018
Hepatic steatosis in ob/ob mice; Liver	Suppressed	Increased GFP-LC3 puncta, LC3- II/LC3-I and p62, decreased proteolysis	Inami, et al., 2011
High fat diet-induced insulin resistance; Liver	Suppressed	Decreased RFP-GFP-LC3 puncta,LC3- II/LC3-I and increased p62	Qian, et al., 2018
High-fat diet-induced insulin resistance; Hypothalamus	Suppressed	Decreased Atg7, Atg5, andLC3-II	(Meng & Cai, 2011)
Palmitic acid-induced insulin resistance; Cardiomyocytes	Enhanced	Increased GFP-LC3 puncta, LC3-II, decreased Atg12-Atg5, Atgl6Ll, Atg3	(S. Li, H. Li, et al., 2017)
Insulin resistance and diabetes in high-fat diet fed mice and db/dbmice; Pancreatic ß cells	Enhanced	Increased autophagosome formation by TEM and LC3-II	Ebato, et al., 2008
Type 1 diabetes in streptozotocin-injected mice; Hearts	Suppressed	Decreased LC3-II, At g 12, and the Atg12-Atg5 complex	(Z. Xie, et al., 2011; X. Xu, Kobayashi, et al., 2013)
Insulin resistance in fructose-fed mice; Heart	Enhanced	Increased LC3-II, Beclin 1, andp62	Mellor, et al., 2011
Type 2 diabetes in human; Heart	Enhanced	Increased LC3-II, Beclin 1, and decreased p62	Munasinghe,et al., 2016
Type 2 diabetes in high fat-fed and streptozotocin-treated mice; Pancreatic ß cells	Decreased	Decreased Atg5 andLC3-II	(M. Fan, et al., 2018)
Type 1 diabetes in streptozotocin-treated mice; Heart	Decreased	Decreased Beclin 1, Atg7, Atg12, LC3- II, and increased p62	(Xiao, et al., 2018)
Change of Autophagy in Obesity and Dyslipidemia			
Obesity in human; Visceral fat	Increased	Increased Atg5 and LC3-II	(Haim, et al., 2015)
Obesity, GFP-LC3+-ob/ob mice; Pancreatic islets	Suppressed	Increased GFP-LC3 puncta, LC3- II/LC3-I and p62, decreased proteolysis	(Quan, et al., 2012)
Obesity, both ob/ob mice and high-fat diet; Liver	Suppressed	Decreased Atg7, Atg5, Beclinl, LC3-II, and increased p62	(Inami, et al., 2011; Qian, et al., 2018; L. Yang, et al., 2010)
Obesity in human: Omental and subcutaneous adipose tissue	Increased	increased Atg5, LC3-II, and Atg12-Atg5	(Kovsan, et al., 2011)
Change of Autophagy in Hypertension			
Rat PASMCs, Pulmonary arterial hypertension treated with Chloroquine	Suppressed	increased expression of LC3B-ÏÏ and ATG5 mRNA , increased p62 and BMPR-II protein levels	(Long, et al., 2013)
Mice, cardiac hypertrophy induced by TAC, heart failure	Early suppressed, Late upregulated	decreased LC3-II levels, increased LC3- II levels	(A. Nakai, et al., 2007)
Hypertension in obese ZDF rat; Mesenteric arterioles	Increased	Increased Atg5, Atg7, Beclin 1, p62 and LC3-II	(Q. Dong, et al., 2017)
Stress-induced hypertension in rats; neurons of the rostral ventrolateral medulla	Impaired	Increased LC3-II and p62, and blocked autophagic flux	(Du, et al., 2017)

Table 2:

FDA approved drugs with a known indication on metabolism that may taget autophagy

Drug Name	***Primary Mechanisms of Action***	***Indication***	***Reference***
Carbamazepine	Reduces inositol and Ins(l,4,5)P_3 levels	Liver disease, dwarfism	(Hidvegi, et al., 2010; C. W. Lin, et al., 2013; Mullan, et al, 2017)
Chloroquine	Blocks lysosome-autophagosome fusion and lysosomal protein degradation	Rheumatoid arthritis and autoimmune diseases, cancer?	(Morgan, ét al., 2014; Parkhitko, et al, 2011)
Empagliflozin	SGLT2 inhibitor, AMPK-dependent inhibition of mitochondrial fission	Diabetes	(Zhou, étal., 2018)
Erlotinib hydrochloride	Inhibits the PI3K-AKT-mTOR signaling pathway	Non-small cell lung Cancer	(Gorzalczany, et al., 2011; W. Han, et al., 2011)
Everolimus	Inhibits mTOR signaling	Atherosclerosis, myocardial information and cardiac remodeling	(Martinet, ét al., 2014)
Ezetimibe	Cholesterol absorption inhibitor	Steatohepatitis	(S. H. Kim, ét al., 2017)
Ghrelin	Inhibits mTOR signaling	Diabetes, liver disease	(Chung, Choi, & Park, 2018; Ezquerro, Fruhbeck, & Rodriguez, 2017)
Liraglutide	Inhibits mTOR signaling	Diabetes, liver disease	(Q. He, et al., 2016)
Metformin	Upregulates AMPK	Type 2 diabetes	(Jiang, ét al., 2014); (Kalender, et al , 2010)
Pioglitazone	Inhibits mTOR signaling	Type 2 diabetes, obesity, insulin resistance	(Matsuura, et al., 2015)
Rapamycin (and Rapalogue, CCI-779)	Inhibits mTORCl	Cancer, Metabolic disease	(Majumder, et al., 2004; Morgan-Bathke, ét al., 2014)
Resveratrol	Activates sirtuin 1 and inhibits ribosomal protein S6 kinase	Cancer, Metabolic disease	(Armour, ét al., 2009; Opipari, et al, 2004)
Rilmenidine	Reduces cAMP levels	Huntington's disease	(F. Lin & Qin, 2013; Rose, ét al., 2010)
Trehalose	Increase cardiac	Myocardial Infarction	(Sciarretta, Yee, et al., 2018)
	LC3-II levels, induces autophagy		
Sodium valproate	Reduces inositol and Ins(1,4,5)P_3 levels	Neurodegenerative diseases	(Sarkar, et al., 2005)
Sorafenib	Inhibits mTOR signaling	Cancers	(Prieto-Dominguez, et al., 2016)
Statins	Inhibits geranylgeranyl biosynthesis and activates AMPK	Prostate cancer, squamous cell carcinomas	(L. Ma, Niknejad, Gorn-Hondermann, Dayekh, & Dimitroulakos, 2012)
Trastuzumab	Anti-HER2 antibody (inhibition of HER2, mTOR	Breast cancer, cardiotoxic agent	(Mohan, Shen, Endo, ElZarrad, & Wu, 2016)
Troglitazone	Induces autophagy, apoptosis and necroptosis	Bladder cancer	(S. Yan, et al., 2014)
Rosiglitazone	Reduces autophagy	Traumatic spinal cord injury, traumatic brain injury	(H. Li, et al., 2017; Yao, et al., 2015)
Sitagliptin	Augments or restores autophagy	Diabetic cardiovascular complications	(Dai, et al., 2018; Murase, et al., 2015)
MK-626	Enhances autophagy and restores insulin secretion	High fat diet-induced obesity	(L. Liu, et al., 2016)
GLP-1 analogue	Induces autophagy; inhibits excessive autophagy	Hepatic lipid accumulation; obesity-related glomerulopathy	(H. Guo, et al., 2018; Q. He, et al., 2016)