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Review

Role of autophagy in inherited metabolic and endocrine myopathies

Ying Tan[a,b,1], Yan Gong[c,1], Maolong Dong[a,b,d], Zhaohui Pei[c,*], Jun Ren[b,**]

[a] Department of Emergency Medicine, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China
[b] Center for Cardiovascular Research and Alternative Medicine, University of Wyoming College of Health Sciences, Laramie, WY 82071, USA
[c] The Second Department of Cardiology, The Third Hospital of Nanchang, Nanchang, Jiangxi 330009, China
[d] Department of Burns, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

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ABSTRACT

The prevalence of cardiometabolic disease has reached an exponential rate of rise over the last decades owing to high fat/high caloric diet intake and satiety life style. Although the presence of dyslipidemia, insulin resistance, hypertension and obesity mainly contributes to the increased incidence of cardiometabolic diseases, population-based, clinical and genetic studies have revealed a rather important role for inherited myopathies and endocrine disorders in the ever-rising metabolic anomalies. Inherited metabolic and endocrine diseases such as glycogen storage and lysosomal disorders have greatly contributed to the overall prevalence of cardiometabolic diseases. Recent evidence has demonstrated an essential role for proteotoxicity due to autophagy failure and/or dysregulation in the onset of inherited metabolic and endocrine disorders. Given the key role for autophagy in the degradation and removal of long-lived or injured proteins and organelles for the maintenance of cellular and organismal homeostasis, this mini-review will discuss the potential contribution of autophagy dysregulation in the pathogenesis of inherited myopathies and endocrine disorders, which greatly contribute to an overall rise in prevalence of cardiometabolic disorders. Molecular, clinical, and epidemiological aspects will be covered as well as the potential link between autophagy and metabolic anomalies thus target therapy may be engaged for these comorbidities.

1. Background: cardiometabolic diseases, inherited metabolic and endocrine disorders

The prevalence of cardiovascular and metabolic diseases has increased drastically over the last decades due to an overall rise in the cardiometabolic syndrome, which refers to a cadre of metabolic disorders grouped together in the forms of obesity, insulin resistance and/or type 2 diabetes mellitus, dyslipidemia and hypertension [1–3]. The initial definition for cardiometabolic syndrome by the World Health Organization (WHO) included impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or diabetes mellitus with two or more additional components of hypertension (≥160/90 mm Hg), elevated levels of plasma triglycerides (≥150 mg/dl) and/or low levels of HDL-c (≤35 mg/dl for men and ≤39 mg/dl for women), central obesity [body mass index (BMI) ≥ 30 kg/m^2 or the waist-to-hip ratio ≥ 0.90 for males and ≥0.85 for females] and/or microalbuminuria. A single (sex-specific when relevant) cut-off point was employed then for individual component although practical issues exist such as the need for a hyperinsulinemic euglycemic clamp and validation of correlation between insulin resistance and microalbuminuria. In 2001, the revised criteria by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) suggested three out of the five following indices: obesity (defined as waist circumference ≥ 102 cm in males and ≥88 cm in females [according to the 1998 National Institutes of Health (NIH) obesity clinical guidelines]), fasting glucose ≥ 110 mg/dl, hypertension (denoted as blood pressure ≥ 130/85 mm Hg based on the Joint National Committee guidelines), triglycerides ≥ 150 mg/dl and HDL-c ≤ 40 mg/dl [4]. Nonetheless, this criterion does suffer from certain limitations such as sex discrepancies in healthy HDL-c levels. The prevalence of cardiometabolic syndrome also displays sex and ethnic bias. Hispanics males display the highest prevalence at 34.76% followed by Caucasian (22.91%) and African American males (18.99%). For women, Hispanics present the highest prevalence (28.50%) followed by the African Americans (24.51%) and Caucasians (20.28%)

* Correspondence to: Z. Pei, The Second Department of Cardiology, The Third Hospital of Nanchang, Nanchang, Jiangxi 330009, China.
** Correspondence to: J. Ren, Center for Cardiovascular Research and Alternative Medicine, University of Wyoming College of Health Sciences, Laramie, WY 82071, USA.
E-mail addresses: leak123@126.com (Z. Pei), jren@uwyo.edu (J. Ren).
[1] Equal contribution.

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[5]. African-Americans generally are less prone to cardiometabolic diseases compared to Caucasian although they suffer disproportionately from higher cardiovascular mortality and type 2 diabetes mellitus [6]. The greater cardiovascular risk in African Americans is most likely attributable to non-traditional cardiovascular risk factors such as C-reactive protein (CRP), homocysteine, low density lipoprotein (LDL) oxidation, lipoprotein, adiponectin, and plasminogen activator inhibitor-1 [7]. Native American Indian, Hawaiian, Polynesian and Filipino populations possess a higher risk for the cardiometabolic syndrome compared with individuals of European descent [8]. Data from the NCEP - ATP III criteria revealed a rather high variability in the prevalence in European (10 to 26%) and Indian (7.9 to 46.5%) ethnic groups [8]. However, a much lower rate was noted in Japan with a prevalence of 8.1% in men and 9.9% in women [9]. Although the syndrome as a single entity carries little clinical value itself, it does provide rationales for the recent increase in cardiovascular and metabolic diseases. Current pharmacological treatment of cardiometabolic syndrome is geared towards individual component of the syndrome including dyslipidemia, hypertension and diabetes [10]. In addition, life style modification such as regular exercise and dietary control also displayed some promises as additive measure for the clinical management of cardiometabolic syndrome [11]. A number of pathophysiological mechanisms have been postulated for cardiometabolic syndrome including inflammation, unhealthy life style, lack of physical activity, oxidative stress, mitochondrial injury, culprit genes coding syndromic or non-syndromic monogenic oligogenic or polygenic anomalies and epigenetic factors [12,13]. In addition, many inherited metabolic and endocrine disorders including glycogen storage and lysosomal disorders also participate in the pathogenesis of cardiometabolic diseases [14–17]. These inherited metabolic and endocrine disorders may be rooted from certain inborn errors of metabolism, with characteristic childhood onset endocrine manifestations. Multiple glands may be afflicted including pancreas, thyroid and gonadal glands, leading to endocrine dysfunctions including energy disturbance in respiration, metal (hemochromatosis) and storage abnormalities (cystinosis) [18]. Recent data supported a role for autophagy dysregulation in the onset and development of cardiometabolic disease [3,19–21] and as well as inherited metabolic and endocrine disorders [15,22–24]. Although much progress has been made for the understanding of the complex etiological issues of cardiometabolic syndrome [10,12,13,25], it remains rather challenging for the optimal management of the syndrome possibly due to the multi-factorial contribution of disease pathogenesis. Here we will briefly summarize the likely contribution of various inherited metabolic and endocrine disorders to the overall prevalence of cardiometabolic disease, with a focus on autophagy.

2. Biochemistry, physiology, molecular basis and assessment of autophagy

Autophagy, a dynamic conservative process to remove long-lived, damaged and aggregated cellular components, came from the Greek, ("auto" - oneself, "phagy" – to eat), which refers to a catabolism process for clearance of aged or injured intracellular components to cope up with cell stress and maintain cellular and organismal homeostasis [26]. The ubiquitin-proteasome system (UPS) and autophagy–lysosome systems represent two major forms of proteolytic mechanisms for protein degradation and recycling. Autophagy, however, is different from the UPS pathway in the manner of bulk degradation of intracellular organelles and protein aggregates that is absent for UPS [25]. Up-to-date, three main forms of autophagy are known including macroautophagy, chaperone-mediated autophagy (CMA) and microautophagy [20,27,28]. Microautophagy refers to a process of invagination of lysosomal or endosomal membranes, resulting in the engulfment of cytoplasmic cargo. CMA, on the other hand, is governed by heat shock chaperone of 70 kDa, followed by binding of the pentapeptide KFERQ motif to a lysosomal receptor complex, before the delivery of the complex into lysosome for proteolysis [25]. In macroautophagy or autophagy, cytosolic components are surrounded by double-membranes to form autophagosome, prior to the fusion with lysosomes to degrade the sequestered cargo contents [3]. Typical autophagy process includes initiation, elongation and nucleation, autophagosome formation and maturation, as well as vesicle fusion and autophagosome degradation. Autophagy is also classified into selective or non-selective autophagy depending on the nature of cargo contents – namely axophagy (axons), glyophagy (glycogen), lipophagy (lipids), mitophagy (mitochondria), nucleophagy (nucleus), pexophagy (peroxisomes), reticulopathy (endoplasmic reticulum, ER), ribophagy (ribosomes), xenophagy (intracellular pathogens), and zymophagy (zymogen granules) [25].

Autophagy plays an essential role in the maintenance of cellular homeostasis. Dysregulation of autophagy may participate in the pathogenesis of cardiovascular and metabolic diseases [29]. Regulation of autophagy is accomplished through essential nutrient and energy sensors including mechanistic target of rapamycin (mTOR), AMP-dependent protein kinase (AMPK), and insulin-insulin-like growth factor I (IGF-1) cascade. AMPK and mTOR function as the main positive and negative regulators, respectively, of autophagy through phosphorylation of their downstream target ULK1. In cardiometabolic stress with nutrient excess, hyperactivation of mTOR is perhaps the main "metabolic check-point" for autophagy failure as sustained activation of mTOR complex results in autophagy inhibition and onset of various myopathies [3,30]. In addition to the above-mentioned signaling molecules, a number of receptors, pro-inflammatory cytokines as well as innate and adaptive immune regulators also participate in the regulation of autophagy [31]. Functional autophagy plays an important role in the maintenance of cellular and organismal homeostasis through removal of protein aggregates, lipid droplet and injured organelles, recycling of metabolic components including amino acids, lipids and other metabolic precursors, as well as facilitation of immune response in stress condition such as inflammation through degrading intracellular bacteria and viruses. Lack of autophagy predisposes organisms to metabolic anomalies, inflammation and immune deficiency [25]. Initiation of autophagy in the face of starvation and inflammation inhibits proinflammatory cytokine response, inflammasome maturation and cytokine release [29], validating its unique role in the preservation of cardiometabolic function. Altered autophagy (or autophagy failure) may serve as both causes and consequences for metabolic disorders. Table 1 lists autophagy change in a number of individual components of metabolic syndrome. On the other hand, deficiency in autophagy predisposes to fat diet-induced insulin resistance, obesity and transition into type 2 diabetes mellitus [25]. Table 2 provides the "proof-of-concept" cardiovascular and metabolic pathologies of autophagy overexpression or deletion. As an effective measure to self-replenish energy store upon exhaustion of exogenous resources, autophagy has drawn some great interest in cardiometabolic diseases with nutritional excess such as obesity, insulin resistance and diabetes mellitus [25]. For example, impairment of adipocyte autophagy is present in subcutaneous fat cells from obese patients, resulting in lipid overload and hypertrophy in adipocytes. Such defect may be alleviated following gastric bypass surgery and weight loss, denoting the important role of autophagy in the regulation of adipocyte size and lipid content. In addition, defective autophagy of obese adipocytes may be related to the loss of DAPK2 (death-associated protein kinase 2), a modulator for autophagic flux [32]. Thus, disruption of adipocyte autophagy may contribute to low-grade chronic inflammation, adipose tissue deterioration and lipid accumulation in obesity [32]. It is noteworthy that assessment of autophagy may be challenging and misleading in cases, making examination of autophagy to be somewhat difficult. A rise in autophagosomes suggests either enhanced formation of LC3B or reduced lysosomal clearance (autophagy flux). For better assessment of autophagy flux, protein markers of early autophagosome formation (LC3B) and late lysosomal degradation (p62) need to be evaluated to pinpoint autophagy activity [33]. Typically, increased LC3B along with loss of

Table 1
Examples of autophagy change in cardiometabolic diseases.

Change of autophagy in various cardiometabolic anomalies				
Disease	Organ	Autophagy	Autophagy parameters	Reference
Leptin resistance (standard diet or fructose-rich diet rat)	Adipose tissues and liver	Suppressed/ increased	Decreased Atg7, MAP1LC3b and increased p62 in WAT; increased Atg7 and MAP1LC3b in liver	[94]
Obesity and type 2 diabetes (LETO and OLETF rats)	Liver	Increased	Increased Atg5, Atg6, Atg7 and LC3	[95]
Obesity (standard chow diet or high-fat diet mice)	Liver and heart	Increased/no change	Increased LC3II/LC3I in liver; no change for AMPK and LC3 in heart	[96]
Obesity (t-TUCB, fat-1 mice with transgenic expression of an omega-3 desaturase)	Adipose tissues and liver	Increased	Increased Atg12-Atg5 and LC3-II and reduced p62 in Liver	[97]
Diabetes (Roux-en-Y gastric bypass, diabetic rats)	Liver	Increased	Increased Atg7, Beclin1 and the conversion of LC3	[98]
Insulin resistance (regular diet or high-fat diet)	Liver	Suppressed	Decreased vps34, Atg12 and gabarapl1	[99]
Hepatic steatosis (ob/ob mice, high fat diet mice)	Liver	Suppressed	Increased autophagosome and p62; decreased cathepsin B and L	[100]
Obesity and insulin resistance (ob/ob mice, high fat diet mice)	Liver	Suppressed	Reduced Atg7 protein level and LC3 conversion	[101]
Lipid challenge (regular diet or high-fat diet mice)	Liver	Decreased	Reduced autophagosome/lysosome fusion, inhibited CMA activity; decreased CMA receptor	[102,103]
Model of glycogen storage disease (GSD)Ia (*G6pc−/−* mice)	Kidney	Suppressed	Decreased LC3-II	[77]
Rats with type 2 diabetes mellitus	Vasculature	Decreased	Downregulating autophagy via AMPK/mTOR pathway	[78]
Diabetic cardiomyopathy	Heart	Increased	Increased LC3 II expression and parkin translocation to the mitochondria	[80]
Patients with obesity and type 2 diabetes	Adipose tissue	Increased	Increased LC3-II/LC3-I ratio, up-regulated LC3 and Atg5 mRNA, decreased p62 and mTOR levels	[81]

p62 would denote activated autophagic flux. In contrary, accumulation of LC3B and p62 as seen in our high fat diet model suggests interrupted autophagic flux [34]. The gap in LC3B detected in the presence or absence of lysosomal inhibition refers to lysosomal degradation [26]. Advance in fluorescent microscopy also makes it possible to visualize autophagosomes [green fluorescent protein (GFP)] and autophagolysosomes [red fluorescent protein (RFP)] based on pH value [35].

3. Cardiomyopathy in cardiometabolic syndrome

Cardiometabolic syndrome contributes to cardiac hypertrophy and contractile anomalies [3]. Reduced myocardial perfusion was found in an atherogenic model of cardiometabolic syndrome (including obesity, dyslipidemia and insulin resistance) in swine, with upregulated Atg5 although reduced Beclin1 and LC3BII/I ratio [36]. Using high fat- and/or high cholesterol fed models of cardiometabolic disease, cardiac hypertrophy and contractile anomalies including decreased ejection

Table 2
The effect of altered autophagy on metabolic phenotypes and cardiovascular health.

Genotype	Model	Target organ(s)	Altered autophagy	Influences on metabolic phenotypes and cardiovascular health	Reference
Becn1 overexpression	High glucose	Whole body	Increased	Enhanced cardiomyocyte death	[104]
Becn1 overexpression	Sepsis	Heart	Increased	Improved cardiac function, and alleviated inflammation and fibrosis	[105]
Becn1$^{+/-}$	High glucose	Whole body	Inhibited	Reduced high glucose cardiotoxicity	[104]
Becn1- or Atg16-deficient	Diabetes	Whole body	Suppressed	Improved cardiac function, reduced levels of oxidative stress, interstitial fibrosis, and myocyte apoptosis	[106]
Becn2$^{+/-}$	Regular or HFD	Whole body	Inhibited	Obesity and insulin resistance	[107]
Atg5 overexpression	Regular diet	Whole body	Enhanced	Improved metabolism, reduced blood levels of glucose and increased insulin sensitivity	[108]
Atg5$^{-/-}$	Regular diet	Whole body	Suppressed	Cardiac atrioventricular canal (AVC) defects and *Tbx2* misexpression	[109]
Atg5$^{+/-}$	infused with Ang II or saline	Whole body	Suppressed	Increased ROS production and NF-κB activity, contributing to cardiac inflammation and injury	[110]
Atg7$^{-/-}$	Regular diet	Liver	Inhibited	Increased hepatic lipid accumulation and weight	[111]
Adenoviral *Atg7* knockdown	Regular diet	Liver	Inhibited	Insulin resistance	[48]
Atg7$^{-/-}$	Regular diet	Liver	Suppressed	Reduced hepatic lipid accumulation	[112]
Atg7$^{-/-}$	Regular diet or HFD	Adipose tissue	Decreased	Reduced white adipose tissue mass and enhanced insulin sensitivity	[113,114]
Atg7$^{-/-}$	HFD	Liver	Decreased	Protection against obesity and insulin resistance	[115]
Atg7$^{-/-}$	HFD	Skeletal muscle	Suppressed	Decreased fat mass and were protected from diet-induced obesity and insulin resistance	[115]
Atg7 knockdown	Regular diet	Heart	Decreased	Atrial electrical remodeling and atrial fibrillation susceptibility	[116]
cVps34$^{-/-}$	Regular diet	Muscle	Suppressed	Hypertrophic cardiomyopathy–like cardiomyopathy	[117]
Vps34$^{-/-}$	Regular diet	Liver	Decreased	Decreased glycogen content and increased lipid accumulation	[118]
Atg12$^{-/-}$	High-fat diet	Neurons	Suppressed	Adiposity and reduced energy expenditure	[119]
Atg13$^{-/-}$	Regular diet	Whole body	Suppressed	Atg13-deficient embryos show growth retardation and myocardial growth defects.	[120]
Knock-down of *ULK1* using siRNA	High glucose	H9C2 myoblast cell line	Suppressed	Accentuated high glucose exposure-induced cardiomyocyte injury	[121]
Akt2$^{-/-}$	Aging	Whole body	Enhanced	Protection against cardiac aging	[122]

fraction, fractional shortening, increased ventricular wall thickness, as well as LV end diastolic and systolic diameters (LVEDD, LVESD) were observed [34,37,38]. These changes are accompanied with interstitial fibrosis, build-up of *peri-*/epicardial fat, glucose utilization for energy (a "fetal pattern" as opposed to fatty acids as the main energy source), alterations in the energy sensors, e.g. AMPK, acetyl CoA carboxylase (ACC) and PGC1α in hearts [37]. Possibly functioning as a compensatory response, a transient hyper-activated state in hemodynamics occurred early in cardiometabolic diseases evidenced by elevated cardiac output and blood pressure [36,39] although such hyper-dynamics may become decompensated, leading to cardiac hypertrophy, compromised systolic and diastolic function [39]. Ample of evidence has depicted the presence of heart failure with preserved left ventricular ejection fraction (HFpEF) in obese patients where severe LV systolic dysfunction is rather uncommon [40]. Besides heart failure, atrial fibrillation is another morbidity usually associated with cardiometabolic disease [41]. A number of mechanisms including hemodynamic, neurohormonal activation, lipotoxicity, oxidative stress, apoptosis and inflammation were postulated for the onset and development of cardiac anomalies in cardiometabolic disease [42,43]. More data suggested that compromised autophagy contribute to cardiac dysfunction in cardiometabolic disease [3,38]. This notion received supports from numerous beneficial cardiac effect of autophagy induction in the face of cardiometabolic disease [3,34,44]. Although cardiometabolic disease-induced autophagy failure still warrants further in-depth research, it is plausible to speculate that nutrient sensors capable of regulating adipogenesis, thermogenesis, lipid metabolism, adipokine synthesis and secretion, may drive autophagy as a downstream effector for these biological responses [3,25].

Besides hearts, hepatic energy balance also contributes to dysregulation of autophagy and cardiac function. As a major organ for gluconeogenesis, liver is extremely sensitive to changes in glucogenic amino acids and accumulates fat (steatosis) in the face of obesity and type 2 diabetes, resulting in non-alcoholic fatty liver disease (NAFLD) [45]. Loss- and gain-of-function analysis has confirmed a key role of hepatic autophagy in metabolic disorders. For example, specific deletion of Atg7 in hepatocytes promotes dyslipidemia and hepatomegaly [46,47]. On the other hand, knockdown of Atg7 led to impaired insulin sensitivity and overt ER stress [48], consistent with downregulated hepatic Atg7 in genetic and diet-induced models of obesity. Loss of hepatic autophagy may be due to changes in autophagy genes in insulin resistance or hyperinsulinemia [49]. Impaired autophagy flux was reported in livers from patients with inflammatory hepatic steatosis [50].

Other than hearts and livers, autophagy regulation also contributes to adipogenesis and lipid storage [51]. In physiological setting, nutrient sensors mTORC1 and AMPK function as inhibitor and activator for autophagy, respectively. However, the balance becomes perturbed in metabolic stress [52], such that mTORC1 and AMPK are stimulated and inhibited, respectively, resulting in autophagy failure. Interestingly, elevated autophagosomes was noted in adipocytes derived from obese and diabetic human subjects [53]. Although further study is still warranted, elevated autophagy seems to function as a compensatory mechanism to preserve adipocyte homeostasis through ridding off damaged proteins and organelles under stress. It is noteworthy that excessive autophagy could promote energy storage and facilitate 'self-digestion', leading to autophagic cell death (a term commonly being referred to as "autosis").

Table 1 lists a few examples of changes of autophagy in metabolic active organs. Moreover, mitochondrial integrity also plays a key role in cardiac homeostasis as knockout of Mfn2 gene compromised Parkin-mediated mitophagy, promoted ROS production, leading to heart failure [54]. Loss of mitochondrial membrane potential ΔΨm and mitochondrial damage are common in cardiometabolic disease, which makes mitophagy a unique regulator for mitochondrial quality control through mitochondrial recruitment of dynamin related protein 1 (Drp1) and Parkin for mitochondrial fission and aggregate clearance [55].

4. Autophagy and glycogen storage disease

Massive buildup of autophagosomes is reported in muscle disorders denoting autophagy dysregulation. Autophagic buildup constitutes a main culprit component in cardiac or skeletal muscles, which may interfere with delivery of the therapeutic enzyme [14]. Pompe disease is a form of metabolic myopathy originated from genetic mutation in glycogen degrading lysosomal enzyme acid α-glucosidase (GAA) [56]. In Pompe disease (or glycogen storage disease type II), glycogen-filled lysosomes accumulate in skeletal muscles, due to impaired glycogen breakdown by GAA [14]. Moreover, disturbed intracellular Ca^{2+} homeostasis, mitochondrial Ca^{2+} overload, ROS production, loss in mitochondrial ΔΨm, decreased O_2 consumption and ATP production were also evidence in mitochondria from cardiac and skeletal muscles in Pompe disease [57,58]. L-type Ca^{2+} channel blockers, mTOR regulators and lysosomal enzyme acid α-glucosidase replacement are effective for such lysosomal and neurodegenerative disorders [59,60]. mTOR is a known negative regulator of autophagy, forming two complexes, namely, mTOR complex 1 (TORC1) and mTOR complex 2 (TORC2). Rapamycin-sensitive mTORC1 complex has been well documented to respond to external stimuli (such as nutrient stress), leading to protein synthesis, cell growth and autophagy inhibition [61]. The impairment of autophagy in Pompe disease is likely due to dysregulation of mTOR signaling, in which case reactivation of mTOR signaling using arginine may serve as a target therapy for lysosomal and metabolic dysfunction in Pompe disease [60]. Recent evidence also revealed glycogen accumulation and autophagy failure in lymphocytes, containing PAS-positive vacuoles. Assessment of PAS-positive lymphocytes in the circulation may be indicative for early detection of autophagy vacuolar myopathies and Pompe disease [62]. Lysosomal-autophagosomal fusion is governed by transcription factor EB (TFEB), which functions to resolve autophagic buildup and remove glycogen-filled lysosomes, a hallmark for Pompe disease [63]. Feeney and colleagues found that delivery of TFEB is effective for the removal of enlarged lysosomes, alleviation of autophagic buildup and lysosomal exocytosis, leading to the reduced glycogen storage in Pompe disease. Interestingly, TFEB-offered benefit was negated in autophagy-deficient Pompe mice, denoting an unrecognized role for autophagy in TFEB-governed cellular clearance [15]. The utility of TFEB in Pompe disease received further confirmation from another lab where AAV-mediated TFEB gene delivery alleviated muscle anomalies [64]. Last but not least, TFEB also promotes lysosomal exocytosis in lysosomal storage disorders, including multiple sulfatase deficiency and mucopolysaccharidosis type IIIA. Recent evidence depicted a role for mTOR phosphorylation of TFEB nuclear export [65] although TFEB-related lysosomal and autophagy signaling regulation still remains elusive for inherited metabolic and endocrine disorders.

To elucidate the role of autophagy in glycogen storage diseases, autophagy was evaluated in muscle biopsies and myotubes of early and late-onset glycogen storage disease type II patients with or without enzyme replacement therapy. It is possible that autophagy flux is essential to reconciling maturation of and uptake of GAA, while defect in autophagy contributes to the progression of glycogen storage disease [15]. Enzyme replacement therapy removes lysosomal glycogen readily away from the heart although to a lesser extent in skeletal muscle [66]. Along the same line, report from Nascimbeni and colleagues confirmed the role of autophagy failure in glycogen storage disease and that autophagy flux is important for maturation and uptake of GAA [67,68]. These findings favored the notion of drug development to restore autophagic flux in order to improve enzyme replacement efficacy. In patients, autophagic buildup may damage skeletal muscles with overt autophagosome formation and autophagic buildup in myofibers, in a manner reminiscent of murine models. Further study revealed that poor muscle responsiveness to enzyme replacement therapy may be related to the presence of autophagic debris in Pompe disease. Using an Atg5 muscle-specific inactivation model, autophagy inhibition alone was

able to alleviate the glycogen level by 50–60%. More intriguingly, enzyme replacement therapy in the face of Atg7 knockout lowered muscle glycogen levels to normal levels, something absent in Pompe murine models without autophagy deficiency [66]. To this end, alleviating autophagic buildup or suppression of autophagy may represent a promising target for Pompe disease therapy as well as other diseases with disturbed autophagy.

5. Autophagy and inherited myopathies/endocrine disorders

Autophagy removes aged or injured organelles and protein aggregates, whereas UPS system is essential for protein quality control. Both autophagy and UPS contribute to etiology of muscle wasting in inherited myopathies and muscular dystrophies [69]. Deranged autophagy or UPS function produces detrimental sequelae on muscle integrity. For example, loss of Dysferlin, a transmembrane protein, serves as the causative factor of limb girdle muscular dystrophy type 2B and Miyoshi myopathy (LGMD2B/MM). Intriguingly, autophagy induction using rapamycin suppressed the ER-stimulated autophagosome formation-mediated mutant dysferlin aggregation in the ER [22], contributing to muscular dystrophy as the post-mitotic skeletal muscles are susceptible to aged or injured organelles and aggregation-prone proteins. A clinical trial recently examined the benefit of low-protein nutritional diet (1 year) in skeletal autophagy induction in patients afflicted with COL6/collagen VI-related myopathies (e.g., Ullrich congenital muscular dystrophy and Bethlem myopathy due to COL6 gene mutation). Their findings confirmed utility of the low-protein diet in autophagy induction to benefit patients with COL6 myopathies [70]. These observations support a key role of autophagy induction as a therapeutic target for muscular disorders such as simvastatin-improved skeletal muscle function in muscular dystrophy [71]. It is noteworthy that autophagy also contributes to inherited muscular dystrophy such as Duchenne muscular dystrophy (DMD) and Golden retriever muscular dystrophy (both X-linked disorders triggered by mutation in DMD gene) and inherited neurological disorders such as those caused by repeat expansion mutations (which are tied to at least 22 inherited neurological diseases) [24,72]. As depicted in Fig. 1, more recent data suggested that faulty mitophagy due to defects in the PINK1/Parkin pathway may contribute to dystrophic cardiac defects in DMD [23]. Although the underlying pathophysiology and genetics can be rather complex for these genetic anomalies, autophagy dysregulation, along with the degradation of misfolded proteins, appears to a common mechanistic theme identified among these diseases [73] (also depicted in Fig. 1). Therefore, a thorough mechanistic description of autophagy or mitophagy degradative machinery should offer novel therapeutic targets and remedies for inherited muscle (or perhaps neurological) disorders.

6. Autophagy and metabolic myopathies in lysosomal storage disorders

Lysosome controls catabolic and anabolic processes in response to a cadre of environmental factors including nutrient/energy availability and cell stress [74]. Lysosomal storage disorders denote to a cluster of inherited metabolic anomalies elicited by deficiencies in lysosomal proteins, leading to accumulation of undegraded metabolites, disruption of lysosomal proteostasis and metabolic myopathies [74–76]. Recent findings have revealed an important role for lysosomes in nutrient-dependent biological events such as nutrient sensing, metabolic adaptation, and protein quality control [77]. Small vessel vasculopathy (medial thickening with luminal stenosis due to vascular smooth muscle cell proliferation) may develop in response to aberrant autophagy with deficiency of lysosomal associated membrane protein 2 (LAMP-2) [78]. Central nervous system is afflicted with neuroinflammation resulting from heightened neuronal vulnerability based on post-mitotic state [79]. For example, lysosomal storage of heparan sulfate triggers mitochondrial defects, altered autophagy, and neuronal death in a mouse model of mucopolysaccharidosis III type C [80].

Danon disease is an X-linked disorder that leads to mitochondrial injury, impaired mitophagy, skeletal muscle weakness and severe cardiomyopathy (such as skeletal myopathy and LAMP2 cardiomyopathy) due to deficiency in LAMP2 [81]. In female patients, a more delayed onset and less severe phenotype may be resulted from random inactivation of the X chromosome housing mutant alleles. LAMP-2 deficiency leads to compromised autophagic flux, leading to oxidative stress, and subsequently, cardiomyocyte apoptosis. Removal of free radicals exhibited benefits for patients with Danon disease [82]. A unique Danon disease model based on induced pluripotent stem cells (iPSCs) was produced to evaluate the therapeutic potential of Xi-chromosome reactivation using a DNA methylation inhibitor. This type of iPSC platform is expected to provide new tools for not only mechanistic but also therapeutic insights for X-linked Danon disease [83]. Autophagy condition may be applied to differentiate Danon disease from other forms of inherited myopathies. For example, Sugimoto reported a case (46-year-old man) of the late-onset myopathy and dilated cardiomyopathy with clinical features distinct from the X-linked myopathy

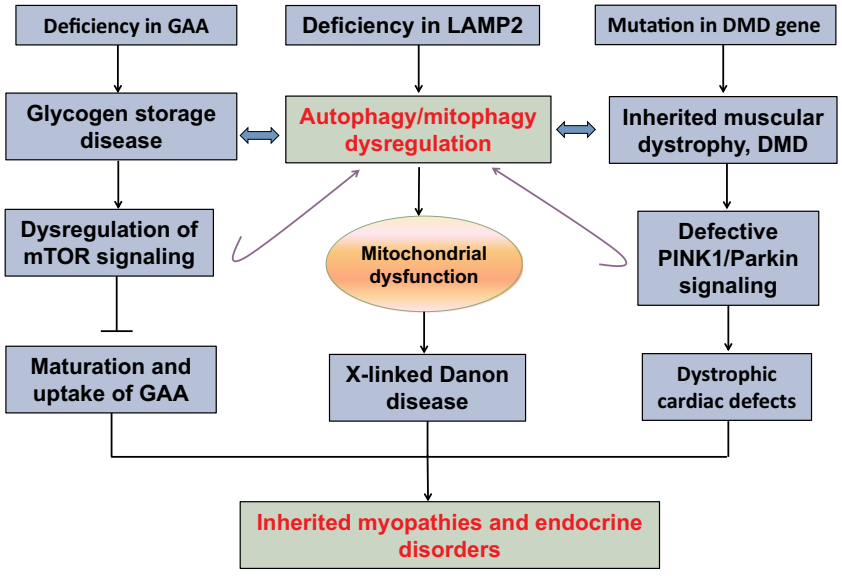

Fig. 1. Autophagy-related mechanisms in inherited myopathies and endocrine disorders. Deficiency in GAA, LAMP2 and DMD lead to metabolic anomalies, resulting in autophagy and mitophagy dysregulation and subsequently aggregation of inherited myopathies and endocrine disorders. GAA: acid α-glucosidase; mTOR: mechanistic target of rapamycin; LAMP2, lysosomal associated membrane protein2; PINK1: PTEN induced kinase 1; Parkin, E3 ubiquitin ligase PARK2; DMD: Duchenne muscular dystrophy.

(Danon disease). This investigator noted excessive autophagy and autophagic vacuolar myopathy [84]. Autopsy and microscopic analyses also revealed existence of extensive intra-lysosomal degradation of mitochondria and other organelles, and distended lysosomes in cardiomyocytes, hepatocytes and smooth muscle cells in a patient with non-Danon disease albeit with a clinical history of cardiac hypertrophy and hypertension. Distended lysosomes suggested ubiquitination in the absence of immuno-detectable p62 (autophagy) formation [85]. Therefore, autophagy status may serve as a relevant marker for differential diagnosis for Danon disease and other forms of myopathies.

Other than inherited lysosomal diseases mentioned above, autophagy may play a role in other comorbidities. X-linked myopathy with excessive autophagy (XMEA) is a rare hereditary childhood-onset disease with compromised proton pump vacuolar ATPase (V-ATPase), as a result of hypomorphic mutation in VMA21 [86]. In consequence, lysosomal pH is elevated, leading to loss of acidic lysosomal hydrolase digestive function and accumulation of autophagic vacuoles with sarcolemmal features (AVSF) [87]. Nonetheless, cardiac structure and function seem to be spared in patients with symptomatic XMEA [88]. Several aspects may be considered. VMA21 is responsible for assembly of V-ATPase, whereas LAMP-2 is associated with multiple functions including endosomal cholesterol transport [89].

Given the ample of clinical and epidemiological evidence denoting a role for autophagy in the maintenance of metabolic homeostasis [3,25], pharmacotherapies on modulation of autophagy have shown some promises in the clinical management of metabolic derangements [25,90] although many drugs suffer from off-target or autophagy-independent effects. For a better review of drugs with autophagy regulating potential in metabolic diseases, please see our recent review [25] for a better and more detailed discussion.

7. Challenges and future perspectives

In summary, accumulating evidence has suggested a role for autophagy in cardiometabolic diseases in particular those originated from inherited metabolic and endocrine myopathies. It is worth mentioning that various mechanisms independent of autophagy also play an important role in inherited myopathies/endocrine disorders. For example, alterations in immune system occur in Duchenne muscular dystrophy, suggesting an involvement of immune defect in muscle death and fibrosis. It is possible that disease-specific immunomodulatory machineries dictate cell damage response under diverse genetic mutations [91]. In addition, autophagic vacuolar myopathy needs to be expanded and perfected at a disease entity. Up-to-date, Danon disease, X-linked myopathy with excessive autophagy (XMEA) and infantile autophagic vacuolar myopathy are the three predominant forms [84]. Relatively limited information is presented here concerning the possible involvement of autophagy defects in the etiology and pathophysiology of inherited and endocrine myopathies, in particularly similarities and differences in autophagy presentation. Perhaps one major challenge at this time is the application of autophagy modulators in these cardiometabolic anomalies. Although pharmacological and non-pharmacological measures such as life style and dietary modification have been proven to benefit cardiometabolic health [92], employment of drugs with selective autophagy regulatory capacity remains a daunting process for the inherited myopathies and endocrine disorders. A more thorough knowledge of the genetic background and resulted metabolic profiles is essential to guide drug development for these inherited metabolic and endocrine anomalies [93].

Transparency document

The Transparency document associated with this article can be found, in online version.

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Conflict of interest

None of the authors had nothing to declare.

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