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# Autophagy as a crosstalk mediator of metabolic organs in regulation of energy metabolism

**Kook Hwan Kim · Myung-Shik Lee**



**Abstract** Autophagy plays an important role in the regulation of cellular homeostasis through elimination of aggregated proteins, damaged organelles, and intracellular pathogens. Autophagy also contributes to the maintenance of energy balance through degradation of energy reserves such as lipids, glycogen, and proteins in the setting of increased energy demand. Recent studies have suggested that autophagy, or its deficiency, is implicated in the pathogenesis of insulin resistance, obesity, and diabetes. These effects of autophagy or its deficiency in regulation of energy metabolism are mediated not only by cell-autonomous effects, such as direct autophagic degradation of energy stores or intracellular organelles (endoplasmic reticulum and mitochondria) but also by non-cell-autonomous effects, such as induction/suppression of secreted factors or changes of sympathetic tone. In the present review, we highlight a recent surge in the research on the autophagy in the regulation of energy homeostasis, with a focus on its role as a mediator for crosstalk between metabolic organs.

**Keywords** Autophagy · Insulin resistance · Non-cell-autonomous effect · FGF21 · Mitokine · IL-1β

## 1 Introduction

Autophagy (derived from the Greek meaning "self-eating") is an evolutionarily conserved catabolic process that delivers intracellular constituents to lysosomes for degradation. Autophagy has been classified into three different types (microautophagy, macroautophagy, and chaperone-mediated autophagy) depending on the choice of the pathway by which the cellular material is delivered to lysosome. In this review, we will focus on macroautophagy (hereafter referred to as autophagy), which involves the delivery of cellular constituents sequestered in double-membrane vesicles (autophagosomes) to lysosomes for degradation. Autophagy was first described to be induced by glucagon during nutrient starvation approximately 50 years ago [1]. However, fundamental insights into the *in vivo* role of autophagy have only been gained during the past 10 years. Studies in the past decade revealed that autophagy plays a crucial role in the physiological processes such as development, differentiation or energy homeostasis, and in the pathological processes such as aging, infection, cancer, neurodegeneration, or metabolic syndrome [2–5].

Type 2 diabetes is one of the most rapidly growing diseases worldwide and develops as a combined consequence of insulin resistance and relative insulin deficiency. Insulin resistance is associated with dysfunction of intracellular organelles, such as mitochondria and endoplasmic reticulum (ER), or with accumulation of excess lipids [6–8]. Since autophagy plays a key role in both mobilization of lipids and proteins and recycling of damaged organelles, a deficiency in autophagy activity causes intercellular accumulation of excess fat, aggregated proteins, and dysfunctional organelles. Such deficiency cascade of autophagy results in deterioration of whole-body energy metabolism and development of metabolic disorders, as suggested in recent papers [9–17]. In contrast, autophagy impairment can also contribute to the amelioration of insulin resistance, obesity and diabetes [18–21]. These different outcomes of autophagy impairment are attributable to the orchestration between cell-autonomous and non-cell-autonomous (endocrine) effects. Here, we briefly highlight molecular mechanism of autophagic process and the role of autophagy in degradation of energy sources such as glycogen, lipids and proteins. We also describe how autophagy in various organs

K. H. Kim · M.-S. Lee (✉)
Department of Medicine and Samsung Advanced Institute for Health Sciences and Technology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong Gangnam-gu, Seoul 135-710, Korea
e-mail: mslee0923@skku.edu

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influences whole-body metabolism, focusing on recent findings investigating the role of autophagy as a mediator of intercommunication between metabolic organs.

## 2 Signaling pathway of autophagy process

The core pathway of mammalian autophagy is tightly regulated by the orchestration of more than 30 autophagy-related (Atg) proteins which participate in the formation of isolation membranes or phagophores, the maturation of autophagosomes, and the fusion between autophagosomes and lysosomes [22]. In mammalian cells, the nucleation of an isolation membrane is initiated by the UNC51-like kinase 1/2 (ULK1/2) complex and the coiled-coil myosin-like BCL2-interacting protein (Beclin1)/class III phosphatidylinositol 3-kinase (PI3K) complex (Fig. 1). In nutrient-rich conditions, mammalian target of rapamycin complex 1 (mTORC1) suppresses the induction of autophagy by interacting with and phosphorylating the ULK1/2 complex (comprising ULK1/2, Atg13, Atg101 and focal adhesion kinase family interacting protein of 200 kDa (FIP200)) [23–25]. Autophagy inducers such as starvation and rapamycin cause the dissociation of the ULK1/2 complex from the mTORC1. Dissociated ULK1/2 complex then enhances the Beclin1/class III PI3K complex activity and produces phosphatidylinositol-3-phosphate (PI3P), which recruits effector proteins such as double FYVE-containing protein 1 (DFCP1) and WD-repeat protein interacting with phosphoinositides (WIPI) to promote the initiation of double-membrane vesicle nucleation at the site of phagophore assembly [26–28].

The expansion of autophagosome is mediated by conjugations of two ubiquitin-like systems (Atg12-Atg5-Atg16 and microtubule-associated protein 1 light chain 3-phosphatidylethanolamine (LC3-PE)). The first pathway involves the Atg12-Atg5 conjugation reaction, which is catalyzed by Atg7, an E1-like enzyme, and Atg10, an E2-like enzyme [29, 30]. Atg12-Atg5 conjugates then interact with Atg16 to form the Atg12-Atg5-Atg16 multimeric complex which acts as an E3 ligase for LC3-PE conjugation and which also plays a crucial role in elongation and closure of autophagosomes [31–33]. The second pathway involves the PE-conjugation reaction of LC3. LC3 is synthesized as a precursor protein, pro-LC3, which is immediately converted to LC3-I by a protease, Atg4 [34, 35]. LC3-I is then conjugated with PE to form LC3-II by the sequential action of Atg7, Atg3, another E2-like enzyme, and of Atg12-Atg5-Atg16, acting as an E3-like enzyme [32, 36]. After processing, LC3-II is localized to the membranes of autophagosomes and participates in the formation of autophagosomes, together with the Atg12-Atg5-Atg16 complex. Mature autophagosomes are then fused to lysosomes to form autophagolysosomes (autolysosomes) where engulfed cytoplasmic materials or organelles are degraded by various types of hydrolytic enzymes including proteases, glycosidases, nucleotidases, and lipases. More details in molecular mechanism of autophagy process have been extensively reviewed elsewhere [22, 37].

## 3 The role of cell-autonomous autophagy in energy metabolism

In nutrient-starved cells or organs, autophagy plays an important role in the maintenance of energy balance through cell-autonomous direct degradation of energy sources engulfed by autophagosome. Although most studies have focused on protein catabolism or protein degradation, recent papers have suggested an important role of autophagy in the degradation of non-protein energy sources such as glycogen and lipid [38, 39]. In this section, we briefly describe the cell-autonomous roles of autophagy in regulation of energy balance.

### 3.1 Protein degradation by autophagy

Autophagy-lysosome system is a major catabolic pathway for protein breakdown in addition to the ubiquitin-proteasome system. In nutrient deprivation, autophagy activates bulk protein degradation to harvest amino acids as a fuel for ATP production through the tricarboxylic acid (TCA) cycle. In addition, two studies using either autophagy-deficient yeasts or oocyte-specific *Atg5*-knockout mice have suggested the importance of autophagy in the supply of amino acids for *de novo* protein synthesis [40, 41]. Autophagic protein degradation also contributes to the removal of protein aggregates or the amelioration of disorders characterized by accumulation of abnormal proteins [42].

In starvation, amino acids (especially, glutamine and alanine) released from skeletal muscle or other tissues are utilized as substrates for gluconeogenesis which occurs predominantly in the liver and to a lesser extent in the kidney [43]. Since skeletal muscle represents a large part of the total protein pool in the body, autophagic protein degradation in skeletal muscle may be important in regulation of blood amino acids during fasting. Despite the increased autophagic activity in skeletal muscle of fasting mice, however, we did not observe any change in serum levels of amino acids, such as glutamine or alanine, in skeletal muscle-specific *Atg7*-knockout ($Atg7^{\Delta SM}$) mice compared to that of control mice after 24 h fasting (Kim et al., unpublished data), implying that protein breakdown by skeletal muscular autophagy may not be important in the regulation of serum amino acid levels in fasting. However, we cannot fully exclude the possibility that autophagy of skeletal muscle does contribute to serum amino acid levels during fasting because *Atg7* deficiency occurs predominantly in fast-twitch (type II) fiber of skeletal muscle and to a lesser extent in slow-twitch (type I) fiber in *Atg7*-floxed ($Atg7^{F/F}$)

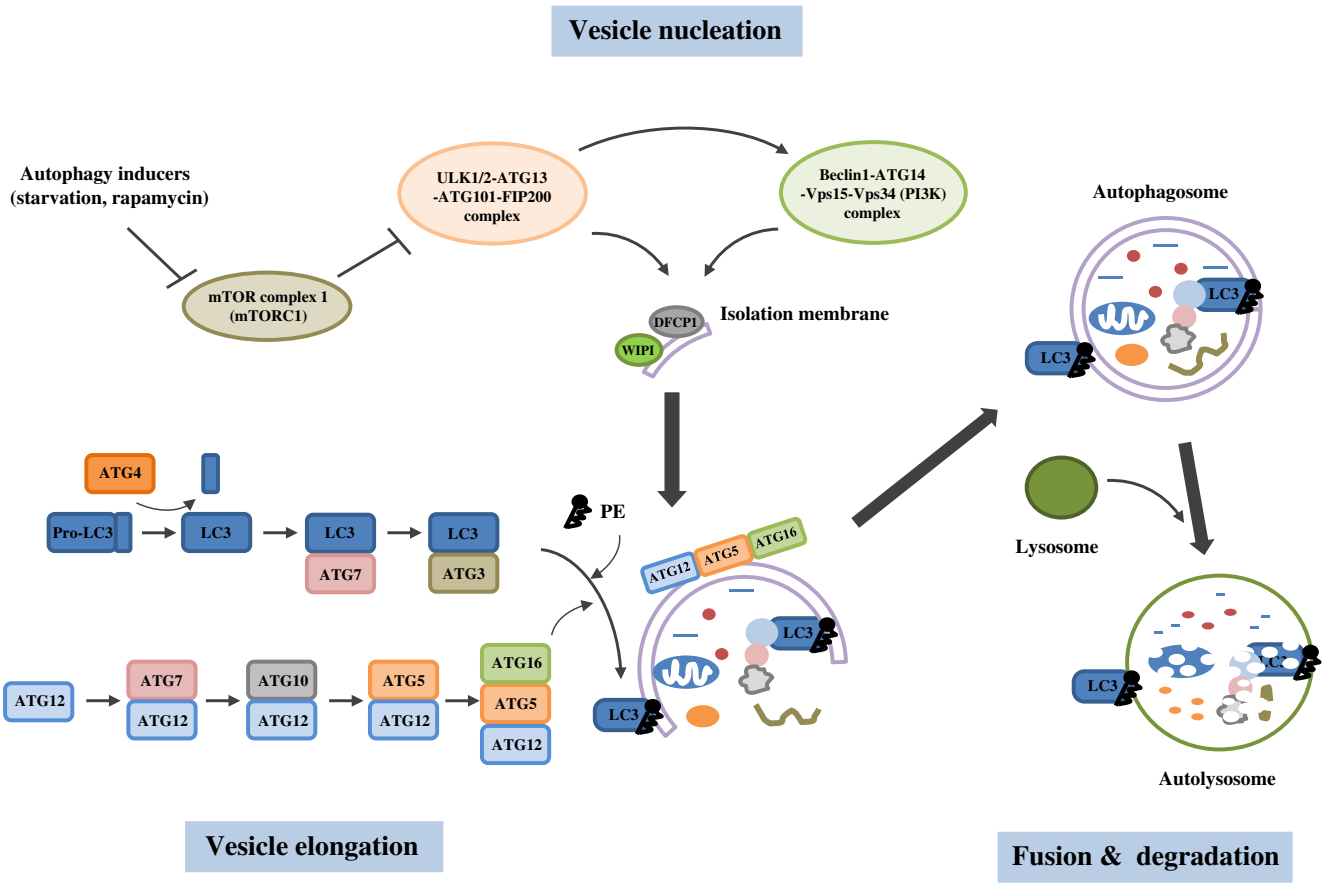


**Fig. 1** The core machinery of mammalian autophagy. Autophagic stimuli such as nutrient deprivation or rapamycin activate the ULK1/2 complex and the Beclin1/class III PI3K complex, both of which are responsible for initiation of autophagy and vesicle nucleation. The vesicle elongation of autophagosome is mediated by conjugated systems of two ubiquitin-like proteins consisting of Atg12-Atg5-Atg16 and LC3-PE. The mature autophagosome then fuses with a lysosome to form an autolysosome wherein engulfed cytoplasmic materials or organelles are degraded

mice expressing Cre under the control of myosin light chain 1 fast (MLC1f) promoter. Intriguingly, a recent study has shown that liver-specific conditional *Atg7*-knockout (*Atg7*$^{F/F}$:Mx1-*Cre*) mice exhibit reduced levels of hepatic/blood amino acids and of blood glucose, when compared to control mice in starvation [44], implying that amino acids released by autophagic proteolysis in the liver contribute to both the maintenance of blood amino acid levels and the regulation of gluconeogenesis. Furthermore, reduced levels of plasma and tissue amino acids have been observed in *Atg5*-null neonate which shows hypoglycemia and neonatal death [45]. Therefore, these results indicate that autophagic proteolysis is an important element in the maintenance of an adequate amino acid pool and of energy homeostasis in nutrient deprivation, although further studies will be needed to evaluate the role of muscular autophagy in the regulation of amino acids.

### 3.2 Glycogen degradation by autophagy (Glycophagy)

In nutrient-rich conditions, glucose is stored mainly in skeletal muscle and the liver as glycogen, which is degraded primarily by glycogen phosphorylase and debranching enzyme during starvation. In addition, glycogen is also degraded by autophagy-lysosome system in the liver and heart tissues of newborn mice [46]. However, a recent paper has shown that utilization and storage of glycogen is normal in hypoglycemic *Atg5*-null neonatal mice [47], suggesting that autophagy may not be a major pathway of glycogen degradation in the neonatal stage of developing mouse. Despite several observations in newborn mice, the role of autophagy in the regulation of glycogen is poorly known in adult mice. Although altered autophagy is observed in vacuolar myopathies characterized by glycogen accumulation, such as Pompe's disease [48], the physiological role of glycophagy in adults has not yet been clarified. Further studies will be needed to evaluate the role of glycophagy in the breakdown of glycogen in adult animals.

### 3.3 Lipid degradation by autophagy (Lipophagy)

In the intracellular environment, triglycerides are stored in lipid droplets. During times of nutrient starvation, cytosolic lipases hydrolyze these triglycerides into glycerol and free

fatty acids (FFAs) which are utilized as energy sources for ATP production through the respective glycerol-phosphate shuttle and β-oxidation pathways. Intriguingly, recent studies have shown that autophagy also participates in the degradation of lipid droplets [49]. In starvation, lipid droplets are engulfed by autophagosomes and transferred to lysosomes in which the lipids are degraded by lysosomal acid lipases. Thus, inhibition of autophagy may lead to accumulation of intracellular triglycerides and decreased ATP production due to the reduced supply of FFAs for β-oxidation.

Recent papers have shown that chronic high fat diet (HFD) or obesity impairs autophagy in various cells and tissues either by blocking the formation of autophagosome and fusion between autophagosome and lysosome, or by inducing lysosomal damage [11, 50–52]. Especially, inhibition of autophagy in the liver by genetic deletion or by obesity causes increased lipid accumulation and/or ER stress due to defective lipophagy or ERphagy, which subsequently leads to the development of hepatic steatosis and/or insulin resistance [11, 49, 53]. Contrary to the expectation of increased lipid accumulation due to deficiency of cell-autonomous effect of autophagy, findings from our recently published study have shown that hepatic lipid content is not increased in HFD-fed liver-specific *Atg7*-knockout ($Atg7^{\Delta Hep}$) mice using albumin-*Cre* system [21]. These discrepancies are probably attributable to non-cell-autonomous effects of autophagy deficiency such as fibroblast growth factor 21 (FGF21) induction in the liver (see Section 4.4 for details). However, metabolic phenotypes of autophagy deficiency may be affected by differences in either the genetic background of the mice or experimental procedures (method of gene disruption or duration of autophagy deficiency). Further studies are required to evaluate the conflicting roles of autophagy in hepatic lipid metabolism.

In contrast, autophagy activity has been reported to be increased in adipose tissue of obese human subjects, probably due to reduced mTOR signaling or increased expression of autophagy-related genes such as Atg5 and LC3 [54–56]. Interestingly, genetic or pharmacological inhibition of autophagy leads to increase of pro-inflammatory cytokines such as interleukin-6 (IL-6) and IL-1β in adipose tissue in correlation to the degree of obesity or adiposity [56]. These results suggest that autophagy may function as a compensatory signal to mitigate obesity-induced pro-inflammatory cytokines and to prevent aggravation of obesity-induced insulin resistance. In contrast, adipose-specific *Atg7*-knockout ($Atg7^{\Delta Ad}$) mice show reduced adipose inflammation and are protected from HFD-induced obesity and insulin resistance [18, 19]. However, it is difficult to completely understand the role of autophagy in lipid-associated inflammation and insulin resistance using the $Atg7^{\Delta Ad}$ mouse model because of the developmental defects of white adipose tissue (WAT) in the mice. Further studies using inducible adipocyte-specific autophagy-knockout mice will be necessary to address this question.

## 4 The role of non-cell-autonomous autophagy in energy metabolism: autophagy as a crosstalk mediator of metabolic organs

Recent studies have highlighted that inter-communication between major endocrine organs, such as adipose tissue, skeletal muscle, liver, islet, and gut, plays a critical role in the regulation of energy metabolism [57–60]. The integrated interactions between the endocrine, nervous, and immune systems also influence the maintenance of whole-body homeostasis [61]. In this section, we describe non-cell-autonomous action of autophagy among various organs related with the three major systems - endocrine, nervous, and immune systems—in the modulation of energy balance.

### 4.1 The role of β-cell autophagy in insulin release

The β-cells produce insulin, which is an endocrine hormone responsible for whole-body glucose homeostasis and anabolism, and β-cell impairment is crucial for development and progression of type 2 diabetes [62]. Intriguingly, it has recently been shown that autophagy in β-cell is altered in Zucker diabetic rats and type 2 diabetic subjects [63, 64]. Moreover, we and others have reported *in vivo* role of autophagy in the maintenance of β-cell mass, structure, and function using mice with β-cell-specific *Atg7* deletion. $Atg7^{\Delta \beta\text{-cell}}$ mice exhibit functional defects in basal and glucose-stimulated insulin release and consequently develop hyperglycemia due to insufficient insulin action in target tissues such as liver, adipose tissue and skeletal muscle [9, 10]. In addition, we have shown that $Atg7^{\Delta \beta\text{-cell}}$ mice develop diabetic phenotype when crossed with *ob* mice [65], suggesting that autophagy deficiency in β-cell could be a factor in the progression of obesity-induced diabetes. Taken together, these results suggest that β-cell autophagy is important in the maintenance of whole-body glucose homeostasis by regulating insulin secretion.

### 4.2 The role of hypothalamic autophagy in the neuropeptides release or sympathetic nerve activity

Hypothalamic neurons play a critical role in the regulation of whole-body energy homeostasis and food intake. The hypothalamic arcuate nucleus (ARC) is composed to two main neuronal populations {anorexigenic proopiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART) neurons and orexigenic neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons} which regulate food intake via communication with the neurons of other hypothalamic regions [66]. POMC/CART neurons inhibit the release of orexigenic neuropeptides such as melanocortin-concentrating hormone (MCH) via the secretion of melanocyte-stimulating hormone (α-MSH) and CART,

leading to suppression of food intake. NPY/AgRP neurons inhibit POMC neuronal activity via the secretion of AgRP, resulting in increased food intake [66]. Thus, exquisite regulation of these pathways is important for control of weight and whole-body energy balance.

A recent study has suggested that obesity or chronic HFD causes the impairment of hypothalamic autophagy via decreased Atg7 and Atg5 protein levels through post-translational modifications [13]. Dysfunctional hypothalamic autophagy has been reported to play a role in obesity-induced hypothalamic inflammation and increased body weight [13]. The role of hypothalamic autophagy in the control of food intake and energy balance has been studied in detail using mice with *Atg7* deletion in AgRP or POMC neurons [12, 14, 15, 20]. $Atg7^{\Delta AgRP}$ mice exhibit decreased food intake and body weight due to increased α-MSH level [20]. In contrast, $Atg7^{\Delta POMC}$ mice show increased food intake, due to the decrease of α-MSH level through impairment of α-MSH generation/secretion, the defective axonal projection of POMC neurons or the impairment of leptin signaling [12, 14, 15]. Intriguingly, $Atg7^{\Delta POMC}$ mice have reduced levels of lipolysis likely due to a decrease of central sympathetic tone acting on peripheral adipose tissues [15]. Thus, increased food intake and reduced peripheral lipolysis contribute to the increased body weight and aggravated glucose intolerance in $Atg7^{\Delta POMC}$ mice. Taken together, these findings indicate that hypothalamic autophagy acts as an important mediator of crosstalk between hypothalamic ARC and other neuron regions or between hypothalamus and peripheral tissues through the regulation of neuropeptides release or sympathetic nerve signal.

### 4.3 The role of macrophage autophagy in IL-1β secretion

Immune systems interact with endocrine and nerve systems in the regulation of energy metabolism. Alteration of diverse types of immune cells, such as macrophages, T cells, B cells, natural killer T cells, neutrophils, eosinophils or mast cells, has been implicated in the development and progression of insulin resistance, obesity, and diabetes [61]. While previous studies of the role of autophagy in immune system have been conducted mainly using pathogen-infected models, a recent study has suggested the importance of autophagy in macrophages in the maintenance of whole-body energy metabolism [67]. Obesity or FFA blocks autophagy in macrophage via inhibition of AMP-activated protein kinase (AMPK)-ULK signaling cascade, resulting in defective mitophagy, increased mitochondrial reactive oxygen species (ROS), and subsequent hyperactivation of NOD-like receptor family, pryin domain containing 3 (NLRP3) inflammasome. Consequently, IL-1β released from macrophages causes impairment of insulin signaling in target tissues such as adipose tissue, liver and skeletal muscle [67]. Consistent with these findings, a recent study has shown that obesity-induced NLRP3 inflammasome activation in macrophages and in adipose tissues contributes to the development of systemic insulin resistance [68]. The results from these studies suggest that autophagy status may affect communication between immune cells and insulin targets tissues. However, detailed studies using macrophage-specific autophagy-deficient mice will be needed to evaluate the role of macrophage autophagy in obesity-induced insulin resistance.

Amyloidogenic human islet amyloid polypeptide (hIAPP) is secreted from islet β-cells and forms toxic oligomers or amyloid fibrils which accumulate in islets of most human subjects with type 2 diabetes [69]. Growing evidence suggests that deposition of amyloid fibrils is correlated with β-cell loss and impaired insulin secretion in this disease [69]. A recent study has shown that NLRP3 inflammasome is activated in hIAPP oligomers-treated macrophages and pancreatic macrophages of hIAPP transgenic mice fed HFD [70]. Considering the previous finding that IL-1 receptor antagonist (IL-1Ra, Anakinra) attenuates hIAPP-induced islet inflammation and β-cell dysfunction [71], hIAPP-induced release of IL-1β from pancreatic macrophages could cause β-cell failure and islet inflammation. Since inflammasome activation is accentuated in autophagy deficiency [67, 72] and hIAPP induces autophagy impairment in pancreatic β-cells [73], autophagy deficiency by hIAPP in macrophages is likely to enhance hIAPP-mediated β-cell injury and inflammation. Intriguingly, IL-1β secretion from hIAPP-treated macrophages is attenuated by cytochalasine D [70], suggesting that phagocytosis is required for hIAPP-induced inflammasome activation. On the other hand, components of autophagic machinery have been reported to contribute to phagocytosis or phagolysosomal process [74, 75], suggesting the possibility that defects of autophagic machinery may downregulate hIAPP-induced inflammation. Further studies will be necessary to understand the role of macrophage autophagy in hIAPP-induced inflammasome activation.

### 4.4 The role of autophagy in skeletal muscle and liver in FGF21 release

Skeletal muscle and liver can affect systemic energy homeostasis by secreting myokines and hepatokines, respectively [58, 60]. We have recently shown that FGF21 released from autophagy-deficient insulin target tissues contributes to the improvement of diet-induced insulin resistance and obesity in $Atg7^{\Delta SM}$ or $Atg7^{\Delta Hep}$ mice [21]. In this subsection, we will briefly address the role of FGF21 in energy metabolism and then describe the effect of autophagy status on FGF21 secretion modulating communication between metabolic organs.

#### *4.4.1 The role of FGF21 in energy metabolism*

FGF21 belongs to FGF family member and is an endocrine hormone expressed predominantly in the liver [76]. FGF21 is

also produced in various peripheral tissues such as WAT, brown adipose tissue (BAT), pancreas, and skeletal muscle [77–79]. The metabolic role of FGF21 was first discovered in an experiment that shows enhanced glucose uptake in 3T3-L1 adipocytes by FGF21 treatment [80]. Subsequently, genetic and pharmacological studies have suggested that FGF21 enhances glucose clearance or lipid catabolism, and improves obesity-induced insulin resistance in diverse diabetic models including obese (*ob*/*ob*, *db*/*db*) mice, Zucker diabetic rats, and diabetic rhesus monkeys [80–83]. The beneficial effects of FGF21 in energy metabolism are attributable to its actions on various metabolic target organs such as adipose tissue [80, 82–86], liver [83, 84, 87, 88], islets [77], skeletal muscle [83, 89], and brain [90]. Thus, these results suggest that FGF21 could be an excellent therapeutic agent in the treatment of type 2 diabetes.

FGF21 expression is tightly regulated in response to alterations in metabolic or energy status; it is induced by fasting and repressed by refeeding, in the liver. In prolonged fasting or ketotic states, proliferator-activated receptor α (PPARα)-mediated hepatic FGF21 induction is required for activation of lipolysis, hepatic lipid oxidation, and ketogenesis [84, 91]. Intriguingly, we have shown that amino acid starvation also results in activating transcription factor 4 (ATF4)-mediated FGF21 induction in the liver, which contributes to the increase of lipid catabolism in adipose tissue in response to amino acid deprivation [21], which is consistent with a recently published study [92]. FGF21 expression is also increased in the liver and adipose tissue of obese mice or obese human subjects [79, 93], although it is not clear whether the increase of endogenous FGF21 is a compensatory mechanism to improve glucose metabolism in obese states or not. These findings suggest that FGF21 plays an important role in adaptive response to various metabolic stresses such as nutrient deprivation and high fat feeding.

#### *4.4.2 The role of FGF21 as a mediator of autophagy deficiency-induced endocrine effect*

In this subsection, we will describe the role of FGF21 in the changes of whole-body metabolism associated with autophagy deficiency which could be considered as a metabolically stressed condition. Based on the importance of skeletal muscle accounting for 80 % of insulin-mediated glucose utilization in the whole body, we have studied the role of muscle autophagy in glucose and lipid homeostasis using $Atg7^{\Delta SM}$ mice. Contrary to our expectation that autophagy deficiency would lead to, or worsen, insulin resistance, $Atg7^{\Delta SM}$ mice exhibit an increase of β-oxidation or lipolysis in WAT, BAT, or liver and have enhanced energy expenditure via thermogenic uncoupling [21]. Consequently, these mice are resistant to HFD-induced steatosis and adiposity, and show improved glucose tolerance and insulin sensitivity (Fig. 2). In microarray analysis, the expression of FGF21 is remarkably upregulated in the skeletal muscle of $Atg7^{\Delta SM}$ mice, when compared to control mice [21]. FGF21 induction is due to mitochondrial impairment-induced ATF4 activation, which is caused by defective autophagy [21]. ATF4-mediated FGF21 expression is also directly induced by mitochondrial respiratory chain inhibitors, such as rotenone and antimycin A, implying that FGF21 could be a 'mitokine' [21], which is consistent with a previous report that FGF21 is produced in muscle of patients with mitochondrial chain deficiency [94]. The term 'mitokine' was first coined by Dillin's group who observed increased longevity

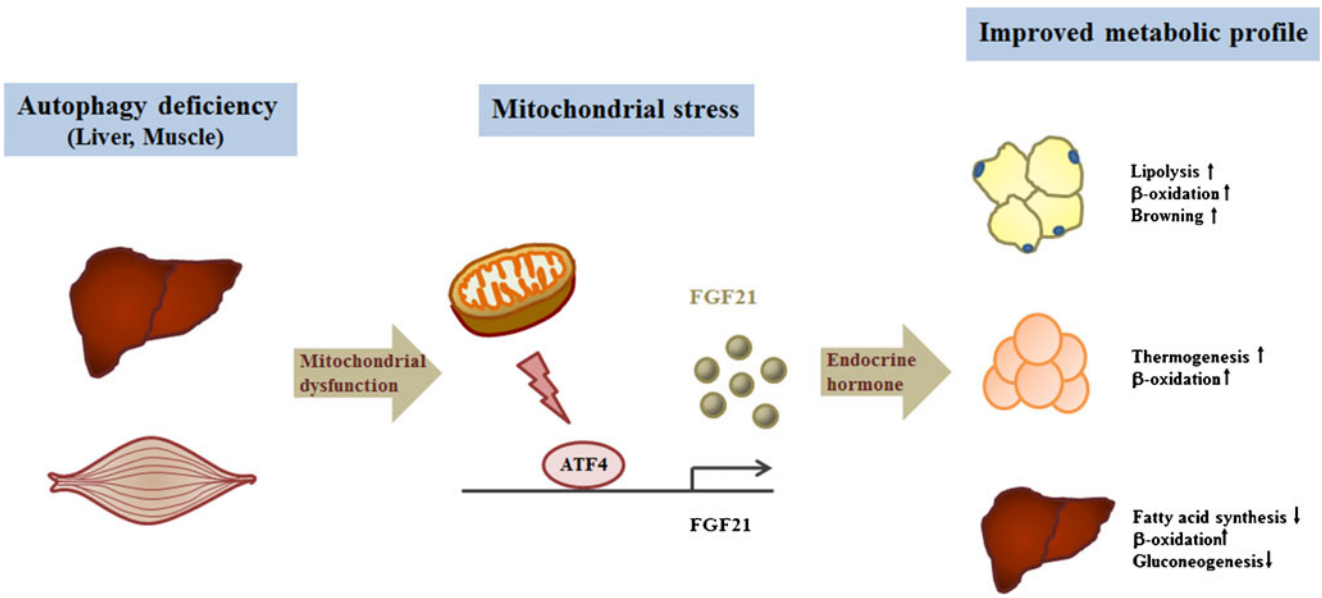


**Fig. 2** The effect of FGF21 induced in autophagy-deficient skeletal muscle or liver tissue on glucose and lipid metabolism. FGF21 acts as a mediator of crosstalk between autophagy-deficient organ and distant metabolic organs in regulation of whole-body energy metabolism

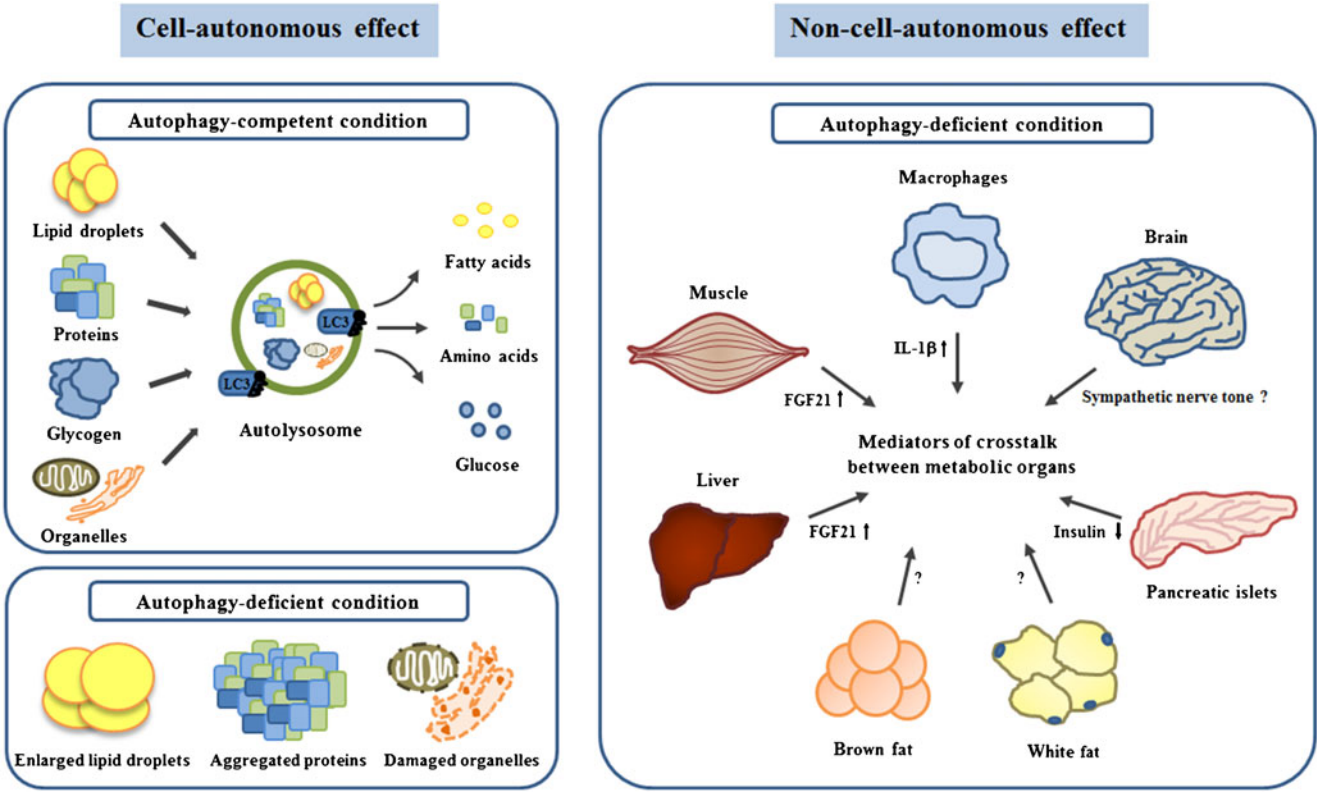


**Fig. 3** Overview of metabolic effects of autophagy and its deficiency. In autophagy-competent condition, autophagy regulates both turnover of organelles and energy balance via removal of damaged organelles and degradation of energy stores (lipid droplets, proteins and glycogen) in a cell-autonomous manner. Inhibition of cell-autonomous autophagy causes accumulation of lipid droplets, toxic aggregated proteins, and damaged organelles (including mitochondria and ER), leading to aggravated metabolic stress and alterations in energy homeostasis. Autophagy deficiency also affects distant organs via non-cell-autonomous routes such as induction/suppression of secretory factors and changes of sympathetic nervous system tone. Thus, autophagy, or autophagy deficiency, in specific organs has different metabolic outcomes, depending on the orchestration between cell-autonomous and non-cell-autonomous (endocrine) effects

of *C. elegans* with disrupted mitochondrial chain activity in central nervous system neurons or intestine [95]. Intriguingly, *FGF21* deletion results in a significant reversal of the reduced fat mass, enhanced glucose tolerance, and insulin sensitivity seen in $Atg7^{\Delta SM}$ mice [21], suggesting that FGF21 acts as a major effector molecule in improved metabolic prolife of these mice. These findings indicate that muscle autophagy status could affect energy metabolism of distant organs and the rest of body via endocrine effects.

Intriguingly, $Atg7^{\Delta Hep}$ mice also are resistant to HFD-induced steatosis and adiposity, and exhibit enhanced glucose tolerance compared to control mice, likely due to enhanced lipid catabolism by increased FGF21 (Fig. 2) [21], similar to the results of $Atg7^{\Delta SM}$ mice fed HFD. These findings are different from suggestions by other investigators that autophagy deficiency causes hepatic lipid accumulation due to impaired lipophagy, which may be attributable to the differences in the method or duration of gene disruption. How does the loss of autophagy cause reduced lipid accumulation despite defects in lipophagy? Reduced supply of lipid from adipose tissue and reduced hepatic fatty acid synthesis may account for such findings. Both of these mechanisms appear to be due to the action of FGF21 that decreases fat mass by increasing β-oxidation/lipolysis and that suppresses lipogenesis. Thus, endocrine effect of FGF21 released from liver tissues lacking autophagy seems to overwhelm cell-autonomous metabolic effects of autophagy deficiency.

Similar to $Atg7^{\Delta SM}$ and $Atg7^{\Delta Hep}$ mice, $Atg7^{\Delta Ad}$ mice are also protected from HFD-induced obesity and glucose tolerance, likely due to increased thermogenesis or β-oxidation in adipose tissue [18, 19]. Since FGF21 is also produced by adipose tissue, it may be worth studying the role of FGF21 in improved metabolic profile of $Atg7^{\Delta Ad}$ mice.

## 5 Conclusion

The emerging evidence suggests that altered autophagy leads to the development of cancer, neurodegenerative disease, and aging. Recent studies also highlight the importance of autophagy in the regulation of whole-body energy metabolism and in the adaptive response to metabolic stress. As discussed in this paper, autophagy deficiency in specific organs causes a broad spectrum of changes in whole-body metabolism, due to both

cell-autonomous and non-cell-autonomous effects of autophagy (Fig. 3). Thus, the role autophagy in energy metabolism is more complicated than expected. Further studies investigating cell-autonomous and non-cell-autonomous metabolic effects of localized or global autophagy deficiency will be required to understand the fundamental metabolic role of autophagy and to develop autophagy-modulating agents for the treatment of type 2 diabetes, obesity, and metabolic syndromes.

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**Conflict of interest** The authors declare no competing financial interests.

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