Targeting autophagy in obesity: from pathophysiology to management

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Abstract | Obesity poses a severe threat to human health, including the increased prevalence of hypertension, insulin resistance, diabetes mellitus, cancer, inflammation, sleep apnoea and other chronic diseases. Current therapies focus mainly on suppressing caloric intake, but the efficacy of this approach remains poor. A better understanding of the pathophysiology of obesity will be essential for the management of obesity and its complications. Knowledge gained over the past three decades regarding the aetiological mechanisms underpinning obesity has provided a framework that emphasizes energy imbalance and neurohormonal dysregulation, which are tightly regulated by autophagy. Accordingly, there is an emerging interest in the role of autophagy, a conserved homeostatic process for cellular quality control through the disposal and recycling of cellular components, in the maintenance of cellular homeostasis and organ function by selectively ridding cells of potentially toxic proteins, lipids and organelles. Indeed, defects in autophagy homeostasis are implicated in metabolic disorders, including obesity, insulin resistance, diabetes mellitus and atherosclerosis. In this Review, the alterations in autophagy that occur in response to nutrient stress, and how these changes alter the course of obesogenesis and obesity-related complications, are discussed. The potential of pharmacological modulation of autophagy for the management of obesity is also addressed.

Owing to the modern lifestyle of high-caloric food intake and reduced exercise, the prevalence of obesity has increased markedly over the past decades and has reached epidemic proportions; over one-third of adults are overweight (BMI 25–29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) worldwide[1–3]. Each year, ~28 million patients worldwide die as a result of complications of overweight or obesity, including hypertension, dyslipidaemia, insulin resistance, stroke, diabetes mellitus, fatty liver disease, coronary heart diseases, cancer and metabolic diseases[4,5]. Treatment of obesity and obesity-related health problems is mainly focused on the control of appetite, blood lipid concentrations and blood pressure. Sibutramine, the most effective agent for weight loss, was withdrawn from the US market owing to cardiovascular safety concerns[6], leaving only orlistat, lorcaserin, phentermine–topiramate, bupropion–naltrexone and liraglutide as the FDA-approved medications for clinical use in addition to nonpharmacological measures such as lifestyle modifications and behavioural therapy[7,8]. Thus, the clinical management of obesity is challenging in the absence of effective medications.

A hallmark of obesity is the accumulation of dysfunctional adipose tissue when energy intake exceeds energy expenditure, which triggers metabolic stress by increasing inflammatory responses and levels of fatty acids, triglycerides and LDL cholesterol, resulting in a cluster of interrelated complications including insulin resistance, glucose intolerance, diabetes mellitus, hypertension, dyslipidaemia, nonalcoholic fatty liver disease (NAFLD), heart failure, atrial fibrillation, musculoskeletal disorders, sleep apnoea, stroke, cancer, Alzheimer disease and pulmonary diseases[9–11]. A plethora of aetiological mechanisms have been implicated in obesity and its complications, including disproportionate or unbalanced food intake and energy expenditure and a complex interplay between genetic and environmental factors that affect haemodynamic, neurohormonal and metabolic regulation, resulting in oxidative stress, inflammation, apoptosis, lipotoxicity, sympathetic overflow of catecholamines and, more recently, alterations (enhancement or suppression) in autophagy, a cardinal process for the regulation of cellular metabolism and energy homeostasis[12–14].

Autophagy is an evolutionarily conserved, lysosome-dependent catabolic process whereby long-lived or damaged proteins and organelles are degraded and recycled for the generation of ATP and new organelles[15–18]. Although basal autophagy is essential for the maintenance of cellular and organismal homeostasis, aberrant changes (increases or decreases) in autophagy contribute

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Key points

- Autophagy regulates cellular energy as well as amino acid, glucose and lipid metabolism; conversely, levels of ATP, amino acids, fatty acids and glucose govern autophagy regulation.
- Autophagy might be either enhanced or suppressed in obesity owing to dyslipidaemia or overnutrition, respectively, and dysregulation of autophagy promotes the onset and development of metabolic disorders.
- Dysregulation of autophagy exhibits tissue specificity and chronological biphasic changes throughout the course of overnutrition and, consequently, obesogenesis.
- Loss of autophagy homeostasis in adipose tissue (for example, diminished adipocyte autophagy despite elevated expression of autophagy genes) has unfavourable effects on local and/or global metabolism that promote metabolic disorders.
- Lifestyle modification (such as exercise and dietary restriction) and pharmacological modulation of autophagy have been proved beneficial for the prevention and treatment of obesity and its complications.

to the pathogenesis of various human diseases, including cancer, cardiovascular diseases, obesity, diabetes mellitus and ageing[17]. In particular, altered (enhanced or suppressed) autophagy has been reported in patients with obesity and animal models of genetically predisposed or diet-induced obesity[19–27]. As discussed in this Review, assessment of the changes in autophagy that occur with obesity can be rather complicated (BOX 1), as they depend on the nature, duration and models of obesity used, the tissue or cell types tested or simply the autophagy monitoring techniques used[28,29]. In addition, inconsistencies in autophagy are frequently encountered during obesity (BOX 2). By contrast, global and tissue-specific deletion and/or mutation of certain autophagy genes or autophagy regulatory molecules result in altered lipid metabolism, hepatic steatosis and an obese or diabetic phenotype in animal models[30,31], supporting a pivotal role for autophagy in the development of obesity (obesogenesis) and obesity-related complications. It is well known that fluctuations in essential metabolic parameters — including levels of amino acids, glucose and lipids — might function as nutrient sensors for the regulation of autophagy and, subsequently, cellular metabolism, insulin sensitization, cell survival, adipogenesis and organ function[16,30]. A complex interconnected cascade of signalling networks can be activated downstream of these metabolic sensors to coordinate autophagic responses to maintain cellular and organismal homeostasis and function[16]. Conversely, the autophagy process itself can generate new amino acids and lipids[30], thereby creating a negative feedback mechanism for the regulation of autophagy (BOX 3 lists examples of the reciprocal regulation between autophagy and metabolism).

In this Review, we summarize the aberrant changes in autophagy that occur with obesity, how nutrient and metabolic stress in obesity signal to influence autophagy and how changes in autophagy gene expression influence obesogenesis and the propensity of excess adiposity. We give particular emphasis to whether changes in autophagy alter the course of obesogenesis and the complications of obesity or whether alterations in autophagy homeostasis are a main consequence of obesity. Finally, the potential of currently available pharmacological and nonpharmacological measures targeting autophagy in the management of obesity and obesity-related metabolic diseases will be addressed.

Autophagy and cellular metabolism

Autophagy (originating from the Greek words auto, meaning 'oneself', and phagy, meaning 'to eat') refers to a conserved process that catabolizes unnecessary and/or dysfunctional intracellular components for quality control in order to attenuate stress and maintain cellular homeostasis[32,33]. Although the term autophagy was first coined in the late 1950s, its mechanism was not described in detail until the mid-1990s as a result of yeast genetic studies[34,35]. Autophagy is a dynamic process with its hallmark being the formation of double-membraned vesicles known as autophagosomes, which first engulf cytoplasmic contents and organelles before fusing with lysosomes to yield autophagolysosomes, where the autophagosomal cargo contents are degraded for the de novo synthesis of ATP and macromolecules[16,17]. Basal autophagy serves as a housekeeping mechanism for the clearance of long-lived or damaged proteins and/or organelles. The presence of cellular stress (for example, starvation, hypoxia and mitochondrial damage) prompts 'self-eating' of injured or aged proteins and organelles to generate ATP and macromolecules[30]. Autophagy selectivity depends on the type of stress; for example, mitochondrial stress promotes autophagy of damaged mitochondria (mitophagy), whereas lipid overload facilitates autophagy of lipid droplets (lipophagy)[30]. Excessive autophagy, however, triggers self-consumption and cannibalistic cell death — a form of nonapoptotic cell death, or type II programmed cell death such as Na^+/K^+-ATPase-regulated autosis[36].

To date, three types of autophagy — microautophagy, macroautophagy and chaperone-mediated autophagy — have been identified on the basis of the modality by which autophagosomes are delivered into lysosomes[29,32,37]. Microautophagy is a process denoting the direct invagination of lysosomal or endosomal membranes, leading to the internalization of cytoplasmic materials into the lysosome[30,32]. Chaperone-mediated autophagy is mediated by the interaction of the pentapeptide KFERQ motif on the substrate protein to heat shock cognate 71 kDa protein (HSC70; also known as HSPA8), which then binds to a lysosomal receptor complex, followed by the unfolding and translocation of the substrate into the lysosome for proteolysis[37]. In macroautophagy, or simply autophagy (the term used hereafter), a double-membraned autophagosome vesicle is formed to sequester cytosolic components, which then fuse with lysosomes to yield autolysosomes, in which the degradation of sequestered cargo contents occurs[15,33,37]. Autophagy is composed of several main operational steps from initiation and phagophore formation to elongation and fusion with endolysosomal vesicles[33]. Macroautophagy is classified into nonselective autophagy and cargo-specific autophagy, the latter of which includes axophagy (axons), crinophagy (secretary vesicles), glyophagy (glycogen), lipophagy (lipids), mitophagy (mitochondria), nucleophagy (nuclei), pexophagy (peroxisomes), reticulophagy (endoplasmic reticulum (ER)), ribophagy (ribosomes), xenophagy (intracellular pathogens) and zymophagy

Nonselective autophagy
Involves the random uptake of portions of the cytoplasm (cytosol and organelles) in the vacuole and/or lysosome for degradation and recycling.

Cargo-specific autophagy
Selective autophagy characterized by a degradation process that is highly regulated by an autophagy receptor, with sequestration cargo specificity for cytoplasmic contents.

Box 1 | **Why is autophagy in obesity confusing?**

- Changes in autophagy might vary depending on the model of obesity (genetically predisposed or environmental factors).
- Changes in autophagy exhibit organ specificity; even in the same model of obesity (such as high-fat-diet-induced obesity), different organs display drastically disparate changes in autophagy.
- Changes in autophagy might be different in the same organ depending on the experimental conditions or techniques for the assessment of autophagy used.
- Changes in autophagy might vary depending on the duration of obesity, the age of patients and experimental animals or the presence of other confounding comorbidities such as type 2 diabetes mellitus.
- Changes in autophagy might be different in vitro versus in vivo (such as the response to hyperlipidaemia in vivo and the use of free fatty acids in vitro).
- Both the pharmacological activation and inhibition of autophagy have proven benefits against obesity and metabolic diseases (only in preclinical studies).
- Changes in the autophagy gold-standard protein marker light chain 3 (LC3) by itself might be misleading depending on the lysosomal function (autophagy flux).
- Changes in autophagy might be different on the basis of the form of autophagy (selective or nonselective) that is being evaluated.
- Changes in autophagy might be either a direct result of adiposity or a compensatory protective response attempting to clear excess lipids. Thus, it is difficult to simply correlate the change in autophagy with a given form of obesity.

(zymogen granules) on the basis of the nature of the cargo for degradation[38,39]. Mitophagy, for example, governs the selective clearance of long-lived or damaged mitochondria through a two-step process including initiation of generic autophagy and selective recognition of the targeted mitochondria for degradation[33,39].

Metabolic molecular mechanisms

Autophagy is regulated by a number of signalling molecules, particularly mechanistic target of rapamycin (mTOR) kinase and the autophagy-related protein (ATG) family, which was originally identified in yeast and has numerous orthologues in eukaryotic cells[16,40]. More than 30 mammalian *ATG* gene products have been found to encode proteins regulating an array of autophagy processes, encompassing the nucleation of autophagic vacuoles to the establishment of autophagosomes and autophagolysosomes[30,33]. Autophagy is highly sensitive to changes in the nutrient environment, cellular metabolism, energy status, hypoxia, oxidative stress, DNA damage, protein aggregates and intracellular pathogens[33] (FIG. 1). Autophagy might be induced by insufficient availability of essential nutrients (including glucose and amino acids) or specific metabolites (including fatty acids and ammonia)[16]. The most important complexes regulating autophagy are the mTOR complex 1 (mTORC1)–ULK1 (also known as ATG1)–ATG13 complex and complexes comprising a class III phosphoinositide 3-kinase (PI3K), such as phosphatidylinositol 3-kinase catalytic subunit type 3 (VPS34; encoded by *PIK3C3*). Activation of mTORC1 induces phosphorylation (and thus, suppression) of the autophagy-initiating ULK1 molecular complex (ULK1–ATG13–ATG17) (FIG. 1). Other than the classic mTOR–ULK1 and PI3K signalling pathways, a number of other cell stress signals, including extracellular-signal-regulated kinase (ERK), JUN N-terminal kinase (JNK) and p53, are also involved in the regulation of autophagy in response to environmental stress[33,41]. Post-translational modifications of ATG proteins, such as phosphorylation, ubiquitylation, nitrosylation, glycosylation, sumoylation and acetylation, as well as transcriptional and epigenetic control mechanisms might also contribute to the regulation of autophagy in stress situations[42]. Conversely, autophagy also governs the levels of essential nutrients through replenishment of the pool of amino acids and the mobilization and hydrolysis of lipid and glycogen stores[37]. Thus, a thorough understanding of the reciprocal regulation of autophagy and macronutrient concentrations is essential for developing strategies to combat obesity.

Amino acids. Amino acids promote cell survival and serve as crucial regulators of autophagy. Food intake transiently increases plasma levels of branched-chain amino acids (BCAAs), including leucine, which subsequently activate mTOR signalling, thereby inhibiting autophagy[43,44] (FIG. 2a). Although long-term malnutrition depletes levels of amino acids, short-term fasting does not deplete amino acids levels owing to reduced protein synthesis and autophagy[44]. In addition, reductions in protein synthesis and amino acid oxidation might lower amino acid demand. During amino acid sufficiency, mTORC1 is activated through a lysosomal vacuolar-type ATPase–ragulator–Ras-related GTP-binding protein (RAG) GTPase complex and the GTP-binding protein RHEB, leading to dissociation of the ULK1 active complex, inhibition of the lipid kinase activity of VPS34 and inhibition of autophagy[30,45]. Indeed, RHEB was found to mediate suppression of cardiac autophagy elicited by diet-induced obesity in mice[45]. In addition to mTOR, eIF2α kinase GCN2 and the autophagy receptor protein sequestosome 1 (also known as p62) also function as amino acid sensors to promote transcription of autophagy genes and RAG GTPase-dependent mTORC1 activity, respectively[30]. Leucyl-tRNA synthetase reportedly functions as a GTPase-activating protein for RAG GTPase and governs BCAA-dependent induction of mTORC1 activation and autophagy inhibition[46]. GCN2 might detect a paucity of one or more essential amino acids to inhibit mTORC1, resulting in autophagy induction[47].

Activation of mTOR as a result of increased growth factor and insulin signalling and/or increased consumption of BCAAs is common in human obesity and in experimental models and is considered to be the main driving force for nutrition-triggered suppression of autophagy[48,49]. BCAAs, which are abundant dietary ingredients that represent ~20% of total protein intake, have a complex role in lowering body weight at the expense of hepatic toxicity[50]. The latter unfavourable effect of BCAAs is attributed to mTOR-dependent inhibition of autophagy, as seen with ageing and obesity[50,51]. During amino acid deficiency or starvation, mTOR activity is suppressed, leading to activation of autophagy and thereby increased intracellular levels of glutamine, in an effort to maintain amino acid balance[30,43]. Nonetheless, the role of certain amino acids (such as glutamine) in the regulation of autophagy has been controversial, as amino acids can activate mTOR through glutaminolysis-produced α-ketoglutarate

Box 2 | **Major inconsistencies and possible explanations for changes in autophagy in obesity**

- Mainstream findings suggest that autophagy is upregulated in adipose tissue, whereas it is mostly downregulated in the liver, heart and pancreas. Differences exist in the regulation of autophagy homeostasis between opposing effects and feedback-loop arms in various organs.
- It is unclear whether adipose tissue autophagy is enhanced or suppressed in obesity or whether altered autophagy is a direct consequence of increased lipid content or a compensatory response trying to reconcile lipid spillover. Increased autophagy in adipose tissue or a given organ in obesity does not necessarily mean that autophagy contributes to the onset and development of obesity and specific organ complications.
- Expression of autophagy genes might not be coordinated with autophagy activity; autophagy flux might be suppressed in adipose tissues during obesity despite increased autophagy gene expression. It is highly probable that post-translational modifications regulate the function of autophagy proteins.
- It is unclear whether autophagy is a mechanism for the elimination of lipid droplets (lipophagy), lipid droplet biogenesis or both (depending on the cell type). Both mechanisms might occur, although the two seem to produce distinct effects on lipid levels.
- The protein levels required to modulate autophagy might not be safe to administer in vivo owing to off-target effects and toxicity. Thus, clinical translation is challenging for the development of autophagy modulators (off-target effect and toxicity).
- It is unclear whether the improvement in metabolic and/or endocrine function with certain drug types (for example, glucagon-like peptide 1 (GLP1) analogues or sodium/glucose cotransporter 2 (SGLT2) inhibitors) is due to the activation or inhibition of autophagy.
- Assessment of autophagy protein markers (such as phosphatidylethanolamine-conjugated light chain 3 I (LC3II)) might not pinpoint changes in a given step of autophagy.
- Autophagosome cargo contents are different (waste versus healthy organelles; tissue and cell-type specificity), which might result in differences in the ultimate cellular fate of autophagy (autosis versus survival).

(resulting in autophagy inhibition) or induce mTOR-independent autophagy through production of ammonia[30] (FIG. 2a). Recent evidence has suggested that the autophagy-induced mTORC1 reactivation is necessary for lysosomal recycling and restoration of protein translation, pinpointing a role for glutamine metabolism in the restoration of mTORC1 activity during amino acid starvation in an autophagy-dependent manner[52].

Disturbance of cellular amino acid pools and homeostasis occurs in obesity, insulin resistance and diabetes mellitus[30,50], which might contribute to dysregulated autophagy in these conditions. However, the precise role for 'resetting and/or reactivation of mTOR' during overnutrition or obesity-induced aberrant changes in autophagy is still unknown. It will be intriguing to discover whether a defect in the 'autophagy reset clock' contributes to obesity and its complications.

Glucose. During states of nutrition excess, elevated levels of plasma glucose activate the insulin–insulin-like growth factor 1 (IGF1) signalling pathway (FIG. 2a) to promote PI3K and protein kinase B (AKT) membrane translocation, leading to phosphorylation (and thus, inactivation) of tuberin (TSC2), which possesses GTPase activity towards the mTOR activator RHEB. As a result, glucose or growth factors promote AKT1-dependent activation of mTOR through inhibition of TSC2–RHEB signalling[44]. During glucose deprivation, ATP levels decrease to promote the accumulation of AMP and activation of AMP-dependent protein kinase (AMPK), a master regulator of autophagy that is activated in response to a rise in the AMP:ATP ratio[32,33]. AMPK can activate autophagy through inhibition of mTORC1 via stimulation of the TSC1–TSC2 (also known as hamartin–tuberin) complex and also directly through phosphorylation and activation of the ULK1 complex[30,44] (FIG. 1). The ULK1 complex then facilitates VPS34 activity and forms structural complexes with essential autophagy components including beclin 1 (also known as ATG6) and ATG14-like protein (ATG14L; also known as ATG14). In addition to the regulation of AMPK, glucose might also promote the formation of a lysosomal vacuolar-type ATPase–ragulator–RAG GTPase complex, which activates mTOR, independently of AMPK[33,44]. Thus, glucose and amino acids share similarity in RAG-dependent activation of mTORC1 (particularly when both are at low levels) during regulation of autophagy[30]. Another key signalling molecule involved in glucose-mediated regulation of autophagy is the forkhead box protein O (FOXO) family of transcriptional factors[53] (FIG. 2a). The NAD^+-dependent sirtuins might deacetylate FOXO to promote autophagy[54]. Finally, not only does glucose tightly regulate autophagy, but autophagy also controls glucose and energy metabolism through the regulation of gluconeogenesis[30].

Lipids. Elevated lipid levels, which occur partly as a result of increased release of fatty acids from dysfunctional and insulin-resistant adipocytes, are common in obesity and might suppress autophagy by interrupting the fusion of the autophagolysosome, lysosomal acidification and hydrolase activity[55]. Indeed, this notion is supported by the findings that elevated lipid content in vitro (by treatment with methyl-β-cyclodextrin) or in vivo (by high-fat diet (HFD) feeding) suppresses autophagosome–lysosome fusion[56]. Intracellular fatty-acid-derived metabolites such as ceramides, diacylglycerol and fatty acyl-CoA might also compromise autophagy homeostasis and contribute to the progression of insulin resistance and steatohepatitis[57]. However, certain free fatty acids (FFAs) such as palmitic acid and oleic acid facilitate autophagy in an interferon-induced double-stranded

Box 3 | **Is altered autophagy in obesity causal or circumstantial?**

- A deficiency in autophagy might not result in a metabolic disease phenotype, although the propensity and the course of obesogenesis or the transition from obesity to type 2 diabetes mellitus or atherosclerosis might be facilitated. This observation is probably due to a loss of the cytoprotective clearance of protein aggregates, lipid droplets and damaged cellular organelles in pathological conditions.
- Autophagy is highly sensitive to changes in nutrient status, particularly high-fat, high-caloric food intake. Obesity or overnutrition might either suppress or promote autophagy depending on the nature and time course of obesity as well as the organ or cell type.
- Changes in autophagy unfavourably influence local (metabolically active organs) or global metabolism, resulting in metabolic derangement either locally or systemically.
- Upregulation of autophagy in obesity in response to inflammatory stimuli or metabolic and endocrine circumstances might serve as a compensatory mechanism to clear protein aggregates, lipid droplets and damaged cellular organelles.
- Mechanistic target of rapamycin (mTOR) activation in response to nutrient excess suppresses autophagy, whereas insulin resistance suppresses activation of mTOR, which in turn could account for the activation of autophagy in adipose tissues.
- Multiple regulatory (and sometimes opposing) signalling pathways are activated in response to changes in the nutrient environment. Inhibition of a given aspect of the metabolic homeostatic balance or changes in the nutrient microenvironment (such as lipid and amino acid levels) might have a unique consequence on autophagy.
- Autophagy might be both a cause and effect of obesity and might create a vicious cycle of metabolic deterioration in obesity and obesity-associated complications.

RNA-activated protein kinase (PKR)–JNK-dependent or mTORC1-dependent manner[58]. In addition, FFAs, including palmitic acid, promote autophagy through mTORC1-independent activation of protein kinase C (PKC)[59]. The apparent reported disparity in the autophagy response to in vivo lipotoxicity (mainly suppressed autophagy) and high in vitro FFA levels (enhanced autophagy), even among various fatty acids in vitro, is somewhat surprising; however, differences in experimental settings, cell or organ types and the degree of saturation of FFAs might contribute to such observations[55]. The FFA-induced autophagy enhancement response has made the use of in vitro cell culture models to recapitulate in vivo obesity somewhat challenging (discussed briefly in BOX 2).

Autophagy might regulate lipid homeostasis through the selective degradation of lipid droplets via lipophagy, control cholesterol transport and maintain energy balance through the intracellular storage and utilization of lipids[60]. Although suppressed autophagy is unlikely to cause lipid accumulation and steatosis by itself, additional factors such as a HFD intake or the presence of gene variants that predispose to obesity might decrease lipid metabolism and promote lipid accumulation[31]. These concepts will be discussed in greater depth in the following section.

Autophagy and obesity

Autophagy is sensitive to changes in nutrient status, particularly high-fat and/or excess caloric dietary intake. More importantly, changes in autophagy might unfavourably influence metabolism locally (in a metabolically active organ) or globally to promote metabolic dysregulation either locally or systemically through endocrine mechanisms. As a result, local metabolic dysregulation might spread rapidly to elicit global metabolic imbalances. Either the enhancement or the suppression of autophagy is seen in metabolic diseases including obesity and diabetes mellitus[19–22], which are possibly attributable to genetic and epigenetic factors, environmental aspects and energy imbalance[61]. For example, dyslipidaemia, high blood pressure and increased blood levels of glucose, which represent three major risk factors in obesity, are believed to be responsible for unfavourable pathological outcomes and changes in autophagy during obesity[62]. Conversely, altered autophagy, particularly a deficiency in autophagy, might promote metabolic dysregulation and obesogenesis[30]. The causal or circumstantial role of altered autophagy in obesity remains rather challenging (BOX 3). In this section, the influence of the major obesity-related risk factors on autophagy, and vice versa, is discussed in detail.

Autophagy in obesogenesis

The role of autophagy in the regulation of obesogenesis is perhaps best illustrated from findings of bioengineered mouse models of gene deletion or overexpression. As summarized in TABLE 1, mice with whole-body or tissue-specific (liver and pancreas) deletion of the *Becn2, Atg7, Lamp2, Tfeb* and *Bif* genes have obesogenic metabolic phenotypes or are predisposed to HFD-induced or genetic (leptin-deficient (*ob/ob*)) obesity[63–67]. For example, liver-specific knockout of autophagy genes *Atg7* and *Tfeb* promoted liver steatosis and weight gain, whereas adenoviral overexpression of *Atg7* and *Tfeb* protected against weight gain and the metabolic syndrome[65,68]. These findings support a key role for autophagy in the mobilization and degradation of lipids and therefore in the regulation of obesogenesis. Consistently, mice with macrophage-specific *Atg7* knockout are more prone to the onset and development of atherosclerotic plaques with the infiltration of lipid-engorged spumous cells[28]. Of note, adipose-tissue-specific *Atg7* deletion reduced white adipose tissue (WAT) mass and improved insulin sensitivity[69,70], suggesting tissue specificity in autophagy-regulated obesogenesis. In addition, liver-specific knockout of *Atg7* in mice was reported to increase[71] and decrease[72] hepatic lipid content through a mechanism associated with clearance (lipophagy) and formation of lipid droplets, respectively. Furthermore, control of autophagy mediated by the central nervous system also contributed to body weight regulation, whereby the inhibition of autophagy in a subtype of neurons producing pro-opiomelanocortin (POMC) promoted the development of obesity by stimulating hyperphagia[73]. In some cases, mice with haploinsufficiency of autophagy genes such as *Atg7* did not display metabolic anomalies in the absence of nutrient stress; however, these mice were predisposed to aggravated insulin resistance and diabetes mellitus when crossed with obese *ob/ob* mice[31,74], favouring the notion that autophagy deficiency disturbs metabolic adaptation during stress. These findings indicate that autophagy insufficiency might facilitate the transition from obesity to diabetes mellitus, therefore highlighting the therapeutic potential of autophagy regulators for prevention and treatment of diabetes mellitus and obesity[74].

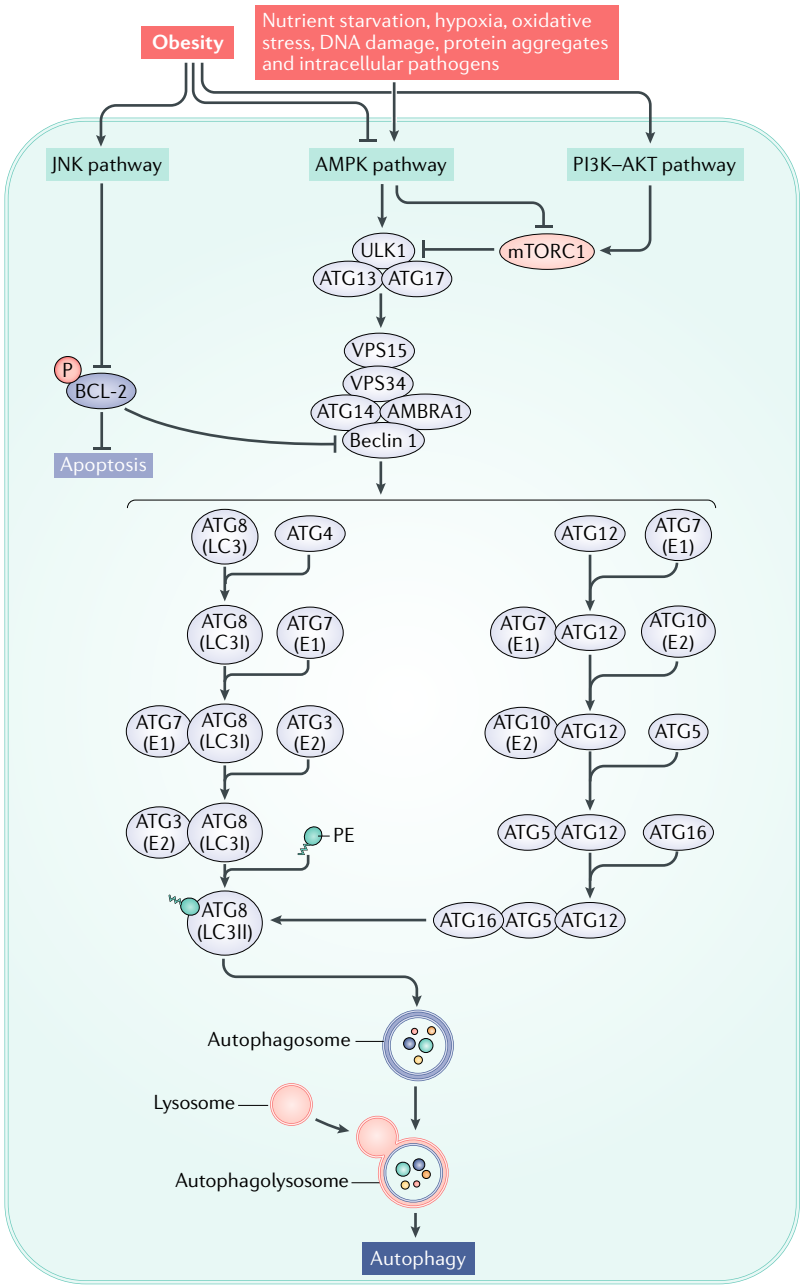

Fig. 1 | **Signalling cascades regulating autophagy during nutrient stress and obesity.** The autophagy signalling cascades are depicted in response to nutrient starvation, hypoxia, oxidative stress, DNA damage, accumulation of protein aggregates, intracellular pathogens and pathological stimuli such as obesity. Typically, AMP-activated protein kinase (AMPK), phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT) and JUN N-terminal kinase (JNK) represent the main cell signalling pathways activated in response to changes in nutrient availability. JNK activation is accompanied by low-grade inflammation in obesity, which triggers phosphorylation of apoptosis regulator BCL-2 to relieve BCL-2-mediated inhibition of the autophagy initiation molecule beclin 1 (also known as autophagy-related protein 6 (ATG6)). Activation of mechanistic target of rapamycin complex 1 (mTORC1) suppresses autophagy through inhibition of the ULK1 complex (comprising ULK1–ATG13–ATG17), which is required for the induction of autophagy. The PI3K–AKT pathway serves as an upstream activator of mTOR, whereas AMPK suppresses mTOR activity or directly activates the ULK1 complex to initiate autophagy. With the induction of autophagy, the activated ULK1 complex recruits the beclin 1–phosphatidylinositol 3-kinase catalytic subunit type 3 (VPS34; encoded by *PIK3C3*) complex to the site of autophagosome formation. ATG14 and PI3K regulatory subunit 4 (VPS15; encoded by *PIK3R4*) might regulate autophagosome formation, possibly via mTOR-independent pathways. Two ubiquitin-like conjugation systems involving ATG proteins regulate the elongation of the double-membraned autophagosome structure. The conjugation of ATG5 to ATG12 involves ATG7 (an E1-like ubiquitin-activating enzyme) and ATG10 (an E2-like ubiquitin-conjugating enzyme), whereas the conjugation of the lipid-conjugated light chain 3 (LC3I; also known as ATG8) to phosphatidylethanolamine (PE) involves ATG4 (a cysteine protease), ATG7 and ATG3 (an E2-like ubiquitin-conjugating enzyme). The ATG5–ATG12 conjugate forms a complex with ATG16, which has E3-like ubiquitin-ligase activity and mediates LC3I–PE conjugation (LC3II). After completion of the double-membraned autophagic vesicles (autophagosomes), the mature autophagosomes fuse with lysosomes to generate autophagolysosomes, where sequestered cargo contents are degraded. AMBRA1, activating molecule in BECN1-regulated autophagy protein 1.

Autophagy and nutrient status in obesity

In obesity, there is an imbalance between increased food intake and inadequate energy expenditure, leading to suppression of autophagy due to increased mTOR signalling[16] (FIG. 2a). During overnutrition, intracellular ATP levels are the main energy source that is synthesized via glycolysis or oxidative phosphorylation, during which NAD^+ serves as an essential substrate for these metabolic processes. Nutrient depletion promotes the accumulation of NAD^+ at the expense of NADH, leading to induction of autophagy through the activity of the sirtuin family of deacetylases[75]. In addition, a decrease in ATP levels, indicative of low energy charge, can induce autophagy through suppression of mTOR[76]. Accordingly, the respiratory chain inhibitor rotenone suppressed mitochondrial ATP synthesis and induced mitophagy (despite inhibiting autophagic flux)[77].

Epigenetic modulation is also involved in the regulation of autophagy in response to nutrient depletion or overnutrition. Recent evidence suggests a crucial role for coactivator-associated arginine methyltransferase 1 (CARM1)-dependent methylation of arginine residues in histones as an essential nuclear event in autophagy, revealing a novel AMPK–S-phase kinase-associated protein 2 (SKP2)–CARM1 signalling axis in induction of autophagy during nutrient starvation[78]. Findings from our recent work showed that an HFD suppressed myocardial autophagy, remodelling and function by dampening calcium/calmodulin-dependent protein kinase type II (CaM kinase II)–AMPK-mediated regulation of the histone-lysine *N*-methyltransferase or histone H3K9 methyltransferase SUV39H[79], further demonstrating the epigenetic regulation of autophagy during nutrient excess. Despite ample evidence suggesting the

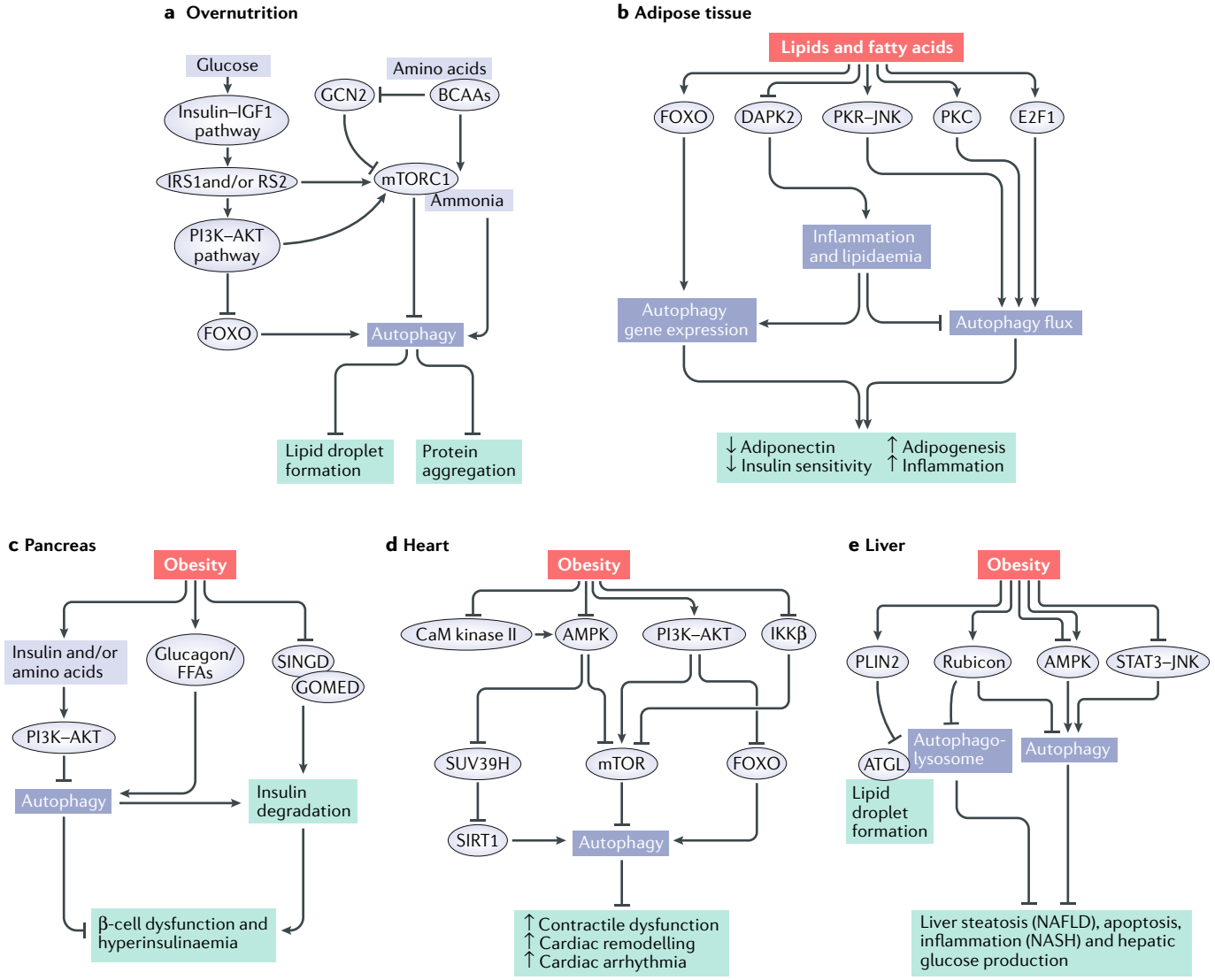

Fig. 2 | **Changes in autophagy in metabolic organs during overnutrition and obesity. a** | Overnutrition status (excess glucose or amino acids) might suppress autophagy through insulin–insulin-like growth factor 1 (IGF1)-mediated activation of insulin signalling pathways (via insulin receptor substrate 1 (IRS1) and/or IRS2 and the phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT) pathway) or through the nutrient sensors mechanistic target of rapamycin (mTOR) or eIF2α kinase GCN2. Activation of PI3K–AKT signalling promotes mTOR activation or inhibits forkhead box protein O (FOXO) transcription factors, resulting in suppression of autophagy. Autophagy might be activated through an ammonia-dependent mechanism. **b** | Obesity-induced increases in lipid and fatty acid levels might stimulate adipose tissue autophagy via stimulation of FOXO, interferon-induced double-stranded RNA-activated protein kinase (PKR)–JUN N-terminal kinase (JNK) signalling, protein kinase C (PKC) and transcription factor E2F1, whereas obesity might inhibit death-associated protein kinase 2 (DAPK2) in adipose tissue. **c** | Pancreatic autophagy might be suppressed during obesity via insulin-driven and/or amino-acid-driven activation of PI3K–AKT signalling. Obesity might also suppress starvation-induced nascent granule degradation (SINGD) and Golgi membrane-associated degradation (GOMED) machineries to reduce the degradation of insulin, leading to an initial compensatory protection against hyperglycaemia but ultimately the onset of insulin resistance. Pancreatic autophagy might also be enhanced by elevated levels of free fatty acids (FFAs) and glucagon in obesity. **d** | Obesity might suppress cardiac autophagy via activation of PI3K–AKT signalling or suppression of phosphorylation of calcium/calmodulin-dependent protein kinase type II (CaM kinase II), AMP-activated protein kinase (AMPK) and inhibitor of nuclear factor-κB kinase-β (IKKβ), leading to increased mTOR complex 1 (mTORC1) signalling and suppression of FOXO activation to favour the inhibition of autophagy. Suppressed CaM kinase II phosphorylation might be responsible for inhibition of AMPK phosphorylation, leading to upregulation of the epigenetic modulator histone-lysine *N*-methyltransferase SUV39H, resulting in suppression of NAD-dependent protein deacetylase sirtuin 1 (SIRT1) deacetylation and autophagy. **e** | Obesity might suppress hepatic autophagy via inhibition of signal transducer and activator of transcription 3 (STAT3)–JNK and AMPK signalling or via stimulation of perilipin 2 (PLIN2) and rubicon. Obesity might also stimulate AMPK to favour hepatic autophagy, the effect of which might be countered by the concurrent inhibitory signalling (such as JNK signalling) in obesity. PLIN2 inhibits the association of lipid droplets with adipose triglyceride lipase (ATGL) and lipophagy proteins. Rubicon interacts with beclin 1 to suppress autophagolysosomes formation. Collectively, loss of cytoprotective autophagy contributes to the accumulation of protein aggregates, lipid droplets and defective mitochondria, which lead to organ dysfunction, insulin resistance and the transition from obesity to type 2 diabetes mellitus. BCAAs, branched chain amino acids; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Table 1 | **The effect of altered autophagy on obesity-related metabolic phenotypes**

Genotype	Target organ or organs	Change in autophagy	Model	Obesity-related metabolic phenotype	Refs
Becn2$^{+/-}$	Whole body	Suppressed	Regular or HFD, mice	Obesity and insulin resistance	63
Atg5 overexpression	Whole body	Enhanced	Regular diet, mice	Improved metabolism, reduced blood levels of glucose and increased insulin sensitivity	219
Atg7$^{+/-}$	Whole body	Suppressed	Bred with *ob/ob* mice	Increased lipid content and increased insulin resistance	74
Lamp2$^{y/-}$	Whole body	Suppressed	HFD, mice	Decreased lipid accumulation and improved hyperinsulinaemic hyperglycaemia and obesity	66
Bif1$^{-/-}$	Whole body	Suppressed	HFD, mice	Adipocyte hypertrophy, obesity and insulin resistance	64
Adenoviral *Tfeb* overexpression	Liver	Enhanced	HFD, mice	Attenuation of weight gain and development of the metabolic syndrome	65
Tfeb$^{-/-}$	Liver	Suppressed	HFD, mice	Increased hepatic lipid content and liver weight	65
Atg7$^{-/-}$	Liver	Suppressed	Regular diet, mice	Increased hepatic lipid content and weight	65
Adenoviral *Atg7* knockdown	Liver	Suppressed	Regular diet, mice	Insulin resistance	68
Adenoviral *Atg7* overexpression	Liver	Enhanced	Bred with *ob/ob* mice	Improved insulin sensitivity	68
Fip200$^{-/-}$	Liver	Suppressed	HFD, mice	Decreased lipid synthesis and reduced hepatic lipid content	220
Vps34$^{-/-}$	Liver	Suppressed	Regular diet, mice	Reduced glycogen content and increased lipid content	221
Atg7$^{-/-}$	Liver	Suppressed	Regular diet, mice	Increased hepatic lipid content	71
Atg7$^{-/-}$	Liver	Suppressed	Regular diet, mice	Decreased hepatic lipid content	72
Atg7$^{-/-}$	Liver	Suppressed	HFD, mice	Protection against obesity and insulin resistance	222
Atg7$^{-/-}$	Pancreas	Suppressed	Regular diet or HFD, mice	Impaired glucose tolerance and reduced insulin secretion	112,113
Atg7$^{-/-}$	Pancreas	Suppressed	Bred with *ob/ob* mice	Hyperglycaemia and diabetes mellitus	111
Atg7$^{-/-}$	Pancreas	Suppressed	HFD, mice	Obesity, elevated blood levels of glucose, glucose intolerance, lower increase in β-cell mass and degenerative changes in pancreatic islets compared with *Atg7fl/fl* mice	223
Vamp7$^{-/-}$	Pancreas	Suppressed	HFD, mice	Mitochondrial dysfunction, loss of insulin secretion and glucose intolerance	116
Atg4b$^{-/-}$	Pancreas	Suppressed	HFD or sucrose fed	Obesity, adipocyte hypertrophy in visceral fat tissue, increased hepatic steatosis, glucose intolerance and attenuated insulin responses	224
Atg7$^{-/-}$	Adipose tissue	Suppressed	Regular diet or HFD	Decreased white adipose tissue mass and enhanced insulin sensitivity	69,70

HFD, high-fat diet; *ob/ob*, leptin-deficient.

existence of epigenetic changes in obesity[13], the epigenetic mechanism regulating autophagy remains unclear in the face of abrupt changes in nutrient availability. Although the role of mTOR in regulating nutrient stress and autophagy has gained attention (FIG. 1), a major gap in our knowledge remains regarding the role of nutrient sensors in the regulation of autophagy in obesity and obesity-related metabolic conditions.

The benefits of limiting food and energy intake in promoting optimal health were supported by a 2017 report that intermittent fasting (60% caloric restriction for 2 days per week or every other day) delays pathological processes through adaptive stress signalling cascades to improve mitochondrial health, DNA repair and autophagy[80]. These findings are in line with the hypothesis that humans and other animals evolved mechanisms to survive in environments where food was scarce and developed adaptations to improve both physical and cognitive functions[30]. In addition to the well-established involvement of mTOR and ATP in the regulation of autophagy, several additional mechanisms involved in energy-restriction-induced autophagy have evolved to cope with adverse environmental conditions. First, nutrient restriction might activate hypoxia-inducible factor 1 (HIF1)[81], which is known to facilitate transactivation of BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) and BNIP3-like (BNIP3L) to stimulate mitophagy[82].

However, direct evidence is still lacking for the role of BNIP3 and ataxia telangiectasia mutated (ATM) in energy-restriction-induced autophagy. Second, nutrient restriction facilitates ATM-mediated TSC2 activation[83] and reactive oxygen species (ROS)-dependent upregulation of autophagic protein ATG4 to promote autophagy[84]. Moreover, caloric restriction alters the levels and/or activity of CoA (the sole donor of acetyl groups), acetyl transferases and/or deacetylases, leading to the induction of autophagy through deacetylation of cellular proteins[85]. Given the availability of multiple pathways that regulate autophagy in response to caloric restriction, the specific signalling cascade that is activated (and therefore the type of autophagy induced) in response to a given nutrient insufficiency, although poorly understood, seems to be crucial. Of note, lysosomal degradation of cytosolic and organelle proteins generates amino acids to sustain protein synthesis or the Krebs cycle to produce ATP and/or glucose, thereby creating an inhibitory feedback loop for the regulation of autophagy[30].

Adipogenesis and lipid metabolism

Ample evidence has indicated an important role for adipose autophagy in the regulation of adipose tissue development, adipogenesis and lipid metabolism[86].

Autophagy in adipocytes. A deficiency in normal autophagy compromises adipocyte differentiation, adipose tissue development and adipokine secretion[86–88]. For example, sequential adipogenic events involving differentiation and mitochondrial energy generation were shown to be regulated by the presenilins-associated rhomboid-like protein (PARL)–PINK1–parkin system, supporting a role for PINK1–parkin-dependent mitophagy at the convergence of metabolic pathology[89]. Obesity is characterized by the accumulation of adipose tissues, and this is often accompanied by increased levels of triglycerides and LDL cholesterol and low levels of HDL cholesterol. The expanded adipose tissue in obesity secretes increased levels of pro-inflammatory adipokines, such as leptin, interleukins and tumour necrosis factor (TNF), and releases decreased levels of the anti-inflammatory adiponectin[88,90]. Pharmacological inhibition of autophagy in human adipose tissue explants resulted in elevated secretion of pro-inflammatory cytokines[24], suggesting an inhibitory role for autophagy in adipose tissue inflammation. Given that obesity is often accompanied by a pro-inflammatory adipose microenvironment in which elevated levels of pro-inflammatory cytokines promote autophagic degradation of microbial pathogens as a compensatory response to combat inflammation, it is unsurprising that increased autophagy and elevated expression of autophagy genes were found in adipose tissues from patients with obesity and experimental animal models[23–25,91]. These data suggest a seemingly 'detrimental' (although probably compensatory) role for autophagy in adiposity; this concept is supported by the clinical and experimental observations that elevated autophagy in adipose tissue is linked with a high-risk obesogenic phenotype defined by visceral fat accumulation and insulin resistance[23–25,87]. Nonetheless, elevated autophagy in adipose tissues in the context of obesity might be associated with increased disposal of intracellular lipids and/or decreased proteolysis[28,92].

A study from 2015 suggested a role for transcriptional regulation of transcription factor E2F1 in visceral (omental) adiposity and resultant metabolic risks, including insulin resistance and increased circulating levels of IL-6 and FFAs, which occur in concert with decreased circulating levels of adiponectin[91]. These associations were weakened following adjustment for autophagy markers ATG5 or light chain 3 (LC3; also known as ATG8), indicating a commonality between elevated expression of E2F1 and autophagy in adipose tissue in obesity (FIG. 2b). The E2F1-null adipocytes were less lipolytic, secreted higher adiponectin and lower leptin levels and were more responsive to insulin and resilient to pro-inflammatory cytokines than E2F1 wild-type adipocytes. Data from the same group later revealed that E2F1 promoted the transcription of apoptosis signal-regulating kinase 1 (ASK1; encoded by *MAP3K5*) in human visceral adipose tissue and experimental animal models, leading to a metabolically detrimental obese phenotype[93]. In addition, E2F1 disturbed adipose endocrine function to connect adipose stress to systemic metabolic dysfunction. However, whether autophagy has a permissive role in E2F1-induced adipose stress resulting in metabolic dysregulation remains unclear. Intriguingly, genetic or pharmacological inhibition of autophagy in adipose tissue or adipocytes from obese mice recapitulated the responses of E2F1 deficiency, leading to adiponectin secretion[94].

Although most of the experimental data implicate elevated adipose autophagy (as summarized in TABLE 2), adipose lysosomal dysfunction was shown to contribute to autophagosome accumulation and early adipose pathologies in obesity[95]. This finding is supported by the observation that attenuated autophagic clearance in adipocytes was associated with the downregulation of the death-associated protein kinase 2 (*DAPK2*) gene in adipose tissue in human obesity[28,92] (FIG. 2b). Thus, adipose tissues in obesity possess increased expression of autophagy genes, albeit with dampened autophagy flux in adipocytes. Measures such as weight loss through bariatric surgery partially reversed compromised autophagy flux by restoring levels of the autophagy regulator DAPK2[28,92]. Considering the notion that inhibition of autophagy increases pro-inflammatory gene expression in adipocytes, it is plausible that elevated adipose autophagy might not simply reflect increased autophagic clearance in adipocytes but might rather be a result of obesity-induced changes in adipose tissue composition. Indeed, high levels of infiltrating immune cells were reported in adipose tissues from individuals with obesity, but not in those from lean individuals[28,92]. Adding to the complexity, mice with a targeted deletion of *Atg7* in adipose tissues displayed reduced fat mass, browning of WAT (loss of white adipocyte differentiation) and resistance to HFD-induced obesity[69,70]. These $Atg7^{-/-}$ mice exhibited improved insulin sensitivity, glucose clearance and increased thermogenic uncoupling or β-oxidation. Increased insulin sensitivity in mice with

Adipokines
Peptide hormones or cytokines secreted by adipose tissues (including leptin, adiponectin and tumour necrosis factor) that have major roles in multiple biological processes such as glucose and fatty acid metabolism, insulin sensitivity and adipocyte differentiation.

Table 2 | **Changes in autophagy in metabolically active organs in obesity**

Model of obesity	Change in autophagy	Autophagy parameters	Refs
Pancreatic islets			
High-fat, high-calorie diet in mice for 12–36 weeks	Suppressed	Decreased expression of LC3II and/or LC3I and ATG7; lysosomal dysfunction; increased phosphorylation of mTOR	114,115,225
HFD intake in Sprague Dawley rats for 16 weeks	Enhanced	Increased LC3, LAMP2 and beclin 1 expression likely due to increased glucagon and FFA	119
HFD in mice for 8–12 weeks	Enhanced	Increased autophagosomes (using GFP-LC3 and electron microscopy)	112,117,118,226
ob/ob mice	Enhanced	Increased autophagosomes (using GFP-LC3 and electron microscopy); increased LC3II	111
High-fat, high-sucrose diet in mice	Enhanced	Increased levels of LC3I and LC3II	227
Liver			
High-fructose diet in rats for 5 months	Enhanced	Increased *Atg7*, *Lamp2* and *Map1lc3b* mRNA expression; p62 protein undetected	163
HFD in mice for 2, 4, 6, 8 and 16 weeks	Early enhanced and late suppressed	Early increase in AMPK activity (4 weeks); late decrease in AMPK activity (16 weeks); late increase in LC3II and/or LC3I expression	173
Spontaneously diabetic obesity (OLETF rats)	Suppressed	Decreased *Atg5*, *Atg6*, *Atg7* mRNA expression; decreased LC3II and/or LC3I expression	165
HFD in mice for 16 weeks	Suppressed	Decreased ATG12–ATG5 levels and LC3II expression; increased p62 expression	228
HFD for 6 weeks, then streptozotocin injection in obese diabetic rats	Suppressed	Decreased ATG7 and beclin 1 expression; decreased LC3I to LC3II conversion	229
HFD in mice for 16 weeks	Suppressed	Decreased chaperone-mediated autophagy with decreased LAMP2 expression	230
HFD in mice for 8, 12, 16, 20 and 22 weeks	Suppressed	Decreased ULK1, beclin 1 and LC3II and/or LC3I expression; decreased *Vps34*, *Atg12*, and *Gabarapl1* mRNA expression; increased polyubiquitin and p62; decreased autophagosome–lysosome fusion; decreased phosphorylation of STAT3 and JNK; increased AMPK phosphorylation	56,68,164,166,231
ob/ob mice	Suppressed	Decreased beclin 1, ATG5, ATG7 and LC3II and/or LC3I expression; increased p62 expression	68,232
Cafeteria diet-induced obesity in rats for 3 months; model of paediatric metabolic syndrome and NAFLD	Suppressed	Decreased LC3II expression and LC3II:LC3I ratio; increased p62 expression	233
HFD-induced NASH or NAFLD model in rats	Enhanced	Increased ATG5 and LC3II expression; increased JNK phosphorylation; decreased phosphorylation of mTOR and p62	234,235
ALIOS diet in mice	Suppressed	Decreased beclin 1 expression; increased LC3I expression	196
Heart			
HFD in mice for 20 weeks	Suppressed autophagic flux	Increased mTOR phosphorylation; increased LC3I, LC3II and p62 expression	139
Atherogenic diet in pigs for 10–16 weeks	Suppressed	Increased mTOR expression; decreased ULK1, beclin 1 and LC3II expression; decreased AMPK phosphorylation; increased ATG12–ATG5 expression	143,144
HFD in mice for 12–22 weeks	Suppressed	Decreased beclin 1 expression; decreased LC3II conversion; increased RHEB and p62 expression; decreased phosphorylation of CaM kinase II, IKKβ, AMPK and TSC2; increased phosphorylation of mTOR	45,79,136,138,145–148
HFD in rats for 8 weeks	Enhanced	Inhibition of mTORC1; increased beclin 1–LC3B–ATG7 expression	149
Adipose tissue			
High-fructose diet in rats for 5 months (WAT)	Suppressed	Decreased *Atg7*, *Lamp2* and *Map1lc3b* mRNA expression; increased p62 expression	163
HFD in mice for 16 weeks (epididymal WAT)	Enhanced	Increased ATG12–ATG5 and LC3II levels; no change in p62 levels	228

Table 2 (cont.) | **Changes in autophagy in metabolically active organs in obesity**

Model of obesity	Change in autophagy	Autophagy parameters	Refs
Obese human adipose tissues (omental, visceral and subcutaneous)	Enhanced	Increased *Atg5*, *Atg7*, *Atg12*, *Lc3a* and *Lc3b* mRNA expression; increased ATG5, ATG12–ATG5, LC3II and p62 expression	23,24,91,236
ob/ob mice (epididymal WAT)	Enhanced	Increased LC3II expression	24
Obese human adipose tissues (visceral and subcutaneous)	Enhanced	Increased immunofluorescence intensity of LC3; increased *Atg5* and *Lc3a* mRNA expression; increased ATG12–ATG5 and LC3II expression; decreased p62 expression	25

ALIOS, American lifestyle-induced obesity syndrome; AMPK, AMP-dependent protein kinase; ATG, autophagy-related protein; CaM kinase II, calcium/calmodulin-dependent protein kinase type II; FFA, free fatty acids; GFP, green fluorescent protein; HFD, high-fat diet; IKKβ, inhibitor of nuclear factor-κB kinase-β; JNK, JUN N-terminal kinase; LAMP2, lysosome-associated membrane glycoprotein 2; LC3I, light chain 3; LC3II, phosphatidylethanolamine-conjugated LC3I; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; *ob/ob*, leptin-deficient; OLETF, Otsuka Long-Evans Tokushima Fatty; STAT3, signal transducer and activator of transcription 3; TSC2, tuberin; WAT, white adipose tissue.

Atg7 deletion in adipose tissue might also be related to mitochondrial or mitokine responses to avoid abnormal deposition of excess lipids and to preserve insulin sensitivity in muscle or liver tissue. However, the precise mechanism by which adipose autophagy is upregulated in obesity remains unknown (BOX 2).

Other than pro-inflammatory cytokines, evidence has also suggested a role for activation of mineralocorticoid receptors in the dysfunctional increase in adipose autophagy during obesity, whereby mineralocorticoid receptor antagonists elicited browning of WAT through correction of autophagy and conversion of WAT into thermogenic fat[88]. Thus, it is tempting to speculate that dysfunctional adipose autophagy contributes to maladaptive adipose tissue expansion, low-grade inflammation and metabolic dyslipidaemia, leading to the onset of obesity-related comorbidities.

Autophagy in nonadipocyte cell types. Of note, the nonadipocyte cell types in adipose tissue might also contribute to regulation of adipose autophagy. For example, dampened autophagy was observed in bone-marrow-derived macrophages from HFD-fed mice[96]. Lysosomal biogenesis in adipose tissue macrophages is required for intra-adipose tissue lipid mobilization in obesity[97]. Macrophage-specific *Atg7*-knockout mice exhibited a shift towards pro-inflammatory M1 macrophage polarization and impaired insulin and glucose metabolism under HFD-fed conditions[98]. In addition, macrophage autophagy is suppressed by inflammatory stimuli, and blockade of autophagy promotes the accumulation of ROS in macrophages[98]. Nonetheless, the mechanism by which autophagy leads to lipid mobilization and metabolism by macrophages is still unknown. A study from 2017 reported that secreted products from adipose tissues interrupted late autophagosome maturation in macrophages, thereby enhancing lipid droplet biogenesis and adipose tissue foam cell formation, ultimately leading to adipose tissue dysfunction in obesity[99]. Evidence also suggests that autophagy is dispensable for macrophage-mediated lipid homeostasis in adipose tissue[100]. Although obesity promotes autophagy in adipose tissue macrophages, genetic or pharmacological inhibition of autophagy does not alter the lipid balance of adipose tissue macrophages[100]. These data are somewhat puzzling as adipose tissue macrophages contribute to both obesity-induced inflammation and metabolic dysfunction.

Obesity increases autophagy in adipose tissues to remove lipid droplets and contributes to lipid catabolism in other tissues. In atherosclerotic plaques, where macrophages accumulate lipids through endocytosis of modified LDL cholesterol, autophagy is required for reverse cholesterol transport[101] and is therefore deemed anti-atherogenic. This observation is in line with an important role for lipid droplet autophagy (lipophagy) in the degradation of esterified lipids. In addition, autophagy of the ER might 'feed' lipid droplets for degradation to cytosolic adipose triglyceride lipase (ATGL; also known as PNPLA2), rather than lysosomal acid lipase/cholesteryl ester hydrolase (LAL), during starvation[102]. Whether autophagy has a functional role (possibly lipid accumulation by phagocytosis of adipocyte remnants and/or de novo lipogenesis) in adipose tissue macrophages remains elusive and warrants further study. In addition, given the potential close and bidirectional links between autophagy and inflammation, it will be intriguing to explore the cell-autonomous immunometabolic contribution to adipose anomalies once altered autophagy is confirmed in adipose tissue immune cells from individuals with obesity[24].

Insulin resistance and diabetes mellitus

Obesity is associated with insulin resistance at multiple levels of insulin signalling, from the intrinsic tyrosine kinase activity of the insulin receptor (IR) to the phosphorylation of IR substrates, as well as downstream kinases, namely, PI3K (metabolic pathway) and MAPKs (growth-promoting pathway)[103]. Insulin levels are regulated by lysosomal degradation of secretory granules via crinophagy, a unique form of autophagy that is dependent on glucose levels[67]. At low concentrations of glucose, crinophagy increases to lower intracellular levels of insulin. Conversely, crinophagy-mediated insulin degradation is inhibited at high concentrations of glucose. However, induction of autophagy in pancreatic β-cells upon starvation promoted the catabolism of nutrients and, subsequently, insulin secretion, which is undesirable for the maintenance of whole-body energy balance and blood glucose homeostasis[30]. A role for starvation-induced nascent granule degradation (SINGD), a form of lysosomal degradation, and

Starvation-induced nascent granule degradation (SINGD). Refers to the lysosomal degradation of nascent secretory insulin granules when β-cells are subjected to glucose deprivation; this process triggers lysosomal recruitment and activation of mTOR to suppress autophagy.

Golgi membrane-associated degradation (GOMED) has been suggested in the maintenance of low insulin levels during fasting[104,105], demonstrating that well-controlled, self-regulatory, noncanonical degradation machinery adapts to nutrient availability (FIG. 2c). These studies have illustrated an essential role for autophagy in the regulation of insulin metabolic signalling, although the effect of obesity on SINGD and GOMED needs to be explored.

Insulin responsiveness might be negatively regulated by pathological influences such as oxidative stress, lipid accumulation, inflammation, ER stress and mitochondrial injury, all of which disturb autophagy homeostasis[103]. As discussed previously, changes in nutrient status influence autophagy, including the upregulation of autophagy due to glucagon production during nutrient deprivation and downregulation of autophagy in states of nutrient excess[32]. Hyperinsulinaemic states compromise autophagy, whereas dampened autophagy can, in turn, disturb insulin metabolic signalling, suggesting a reciprocal regulatory relationship between autophagy and insulin action[88,106]. In addition, hepatic autophagy is impaired in hyperinsulinaemic, HFD-fed and obese *ob/ob* mice, as evidenced by low levels of phosphatidylethanolamine-conjugated LC3I (LC3II) and high p62 levels[107,108]. Decreased autophagy in *ob/ob* mice has been linked to the dampened insulin metabolic signalling and overt ER stress, the effects of which were negated by ATG7 overexpression[68]. These findings suggest a vicious cycle between impaired autophagy and insulin resistance (also discussed in BOX 3).

In both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), persistent hyperglycaemia disturbs the intracellular balance between pro-oxidants and antioxidants, leading to oxidative stress and cellular injury[30,106,109]. Mitochondria are considered the main source of intracellular ROS in diabetes mellitus[13,109]. Increased ROS levels and damaged mitochondrial structure and function are disease hallmarks in patients with T1DM and T2DM and animal models of T1DM and T2DM[109,110]. Autophagy, particularly mitophagy, might be the missing link in the quality control of mitochondria in diabetes mellitus. In addition to its role in waste clearance and ROS production, impaired autophagy might contribute to diabetogenesis through the onset and development of insulin resistance. A potentially important role for autophagy in pancreatic β-cells is the maintenance of metabolic homeostasis; suppression of autophagy by crossing mice with β-cell-specific ATG7 deficiency with *ob/ob* mice promoted hyperglycaemia[111]. Similarly, deficiency in autophagy proteins in β-cells led to the accumulation of damaged organelles, oxidative stress, defective mitochondria and reduced insulin secretion in mice[112,113]. Following HFD feeding in mice, autophagy was either enhanced or suppressed in pancreatic β-cells (TABLE 2). Chronic HFD intake has been shown to suppress autophagy or interrupt autophagy flux in pancreatic β-cells[114,115]. In addition, autophagy-deficient mice were prone to the development of diabetes mellitus with marked mitochondrial damage and β-cell loss upon HFD challenge[111,112,116]. By contrast, increased pancreatic β-cell autophagy has also been reported in mice in response to HFD intake[117–119] or genetic (*ob/ob*) obesity[111]. The observed increase in autophagy activity was suggested to be triggered by lipid accumulation and glucagon production, despite lipid-dependent suppression of protein degradation or proteolysis[111]. Although autophagy protects β-cell function[120], excessive autophagy might be either an adaptive or maladaptive response to regulate β-cell death under conditions of cellular stress[121].

The inconsistencies in the observed obesity-induced changes in β-cell autophagy between studies might be due to the contribution of insulin resistance at the level of mTOR (which will activate autophagy), changes in the microenvironment (amino acids and lipids) and differences in assay methods, models and the duration of obesity. It is believed that insulin-stimulated activation of mTORC1 is responsible for suppression of autophagy in conditions of adequate substrate availability, whereas inhibition of insulin–mTORC1 signalling is responsible for enhanced autophagy during substrate insufficiency[122]. Insulin resistance has been shown to be directly influenced by autophagy in insulin-responsive tissues such as adipose tissue, skeletal muscle, pancreas, liver and brain[69,112,123]. When adipose tissue storage capacity for energy is exceeded, lipids accumulate ectopically in the liver, muscle and heart, promoting tissue-specific insulin resistance in concert with impaired pancreatic function.

Although the reciprocal relationship between autophagy and insulin resistance and/or diabetes mellitus seems to be complex, it is perceived that the pathophysiological changes that occur during insulin resistance disturb autophagy homeostasis and promote the accumulation of dysfunctional organelles such as mitochondria. The loss of the cytoprotective function of autophagy leads to further accumulation of ROS and mitochondrial injury, which contributes to the onset and development of insulin resistance and diabetes mellitus in obesity[124,125].

Autophagy and inflammation in obesity

Obesity is characterized by a state of low-grade systemic inflammation[126–128]. Low-grade inflammation is key to activating an inflammatory programme early in adipose expansion and during chronic visceral adiposity, promoting a pro-inflammatory phenotype of the immune system, favouring the development of insulin resistance and damage to insulin-sensitive organs (such as liver, adipose tissue and heart) and ultimately resulting in metabolic dyslipidaemia[129]. Several highly active adipokines are released during low-grade inflammation, including leptin, resistin, adiponectin or visfatin as well as other classic cytokines such as TNF, IL-6, IL-1 and monocyte chemoattractant protein 1 (MCP1; also known as CCL2)[128,129]. These cytokines promote disparate autophagy responses, including stimulation (for example, adiponectin, leptin and IFNγ) or inhibition (for example, interleukins), depending on the tissue type[130]. A number of stress signalling cascades are activated during low-grade inflammation associated with obesity, including the JNK–activator protein 1 (AP1) complex

Golgi membrane-associated degradation
(GOMED). Characterized by the generation of Golgi membrane-associated structures accompanied by proteolysis and is activated when Golgi-to-plasma-membrane anterograde trafficking is disrupted in autophagy-deficient yeast and mammalian cells.

and nuclear factor-κB (NF-κB) pathways, which also promote different autophagy regulatory responses[130]. Levels of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome are also elevated in obesity and are considered as predominant determinants of obesity-associated inflammation[131]. Although it is well documented that autophagy (mainly mitophagy) controls levels of NLRP3, evidence has indicated that NLRP3 serves as a binding partner of mTOR and that the down-regulation of their interaction promotes autophagy[132]. This is consistent with the consensus of a reciprocal relationship between inflammation and regulation of autophagy.

Many of the cytokines or adipokines released during low-grade inflammation promote autophagy, which constitutes an important mechanism in the elimination of invading pathogens. Conversely, autophagy helps to deactivate the inflammatory response[133]. Although mice with myeloid cell-specific deletion of *Atg7* were metabolically normal, they were predisposed to diabetes mellitus when crossed with obese *ob/ob* mice and displayed upregulation of pro-inflammatory cytokines and inflammasome activation in adipose tissues[31]. Autophagy is believed to protect against inflammation through the clearance of damaged organelles (for example, mitochondria) or intracellular pathogens and the suppression of pro-inflammatory complexes[134]. Although obesity is often suggested to be accompanied by low-grade inflammation, a landmark review from 2016 suggested that obesity promotes pro-inflammatory responses through the activation of calpain or mTOR and inhibition of AMPK in tissues including heart and adipose tissue (FIG. 2b,d), leading to suppression of autophagy flux and ultimately inflammation[133]. Importantly, different effects of certain cytokines (such as IL-6) on autophagy have been reported and depend on the tissue type[133]. In addition, NOD-like receptor (NLR) family members (for example, NOD-, LRR- and CARD-containing 4 (NLRC4) and NLRP4) might negatively regulate autophagy through their association with beclin 1 (REF.[135]). NLRP4 has been reported to interact with the class C VPS complex (comprising VPS11, VPS16, VPS18 and Ras-related protein RAB7) that controls membrane tethering and fusion of vacuolar membranes, thereby blocking the fusion of the autophagosome to the autolysosome[134]. The negative regulatory role of NLR family members in autophagy along with increased NLRP protein levels in obesity suggest a role for increased inflammasome expression and/or activity in obesogenesis and obesity-related organ complications. This notion is supported by our finding that knockout of the gene encoding the NLRP3 adaptor protein caspase recruitment domain-containing protein 9 (*Card9*) rescued mice from obesity-induced loss of autophagy, cardiac remodelling and contractile dysfunction[136]. Thus, inflammasomes might serve as a central hub in the coordination of inflammation and autophagy in obesity. Further investigation is needed to uncover the multiple interactions between autophagy and cytokines (and inflammasomes) to better understand the roles of autophagy in the control of inflammation and fine-tuning of the immune response in obesity.

Obesity-related cardiac dysfunction

Cardiomyopathy develops in obesity and is characterized by structural and functional alterations in the heart and interstitial fibrosis in the absence of coronary artery disease or hypertension[13]. Evidence from our group and others has uncovered a role of suppressed autophagy in the onset and development of obesity-related metabolic cardiomyopathy[137–139]. Autophagy helps to meet metabolic requirements in the heart during pressure overload, hypertension and ischaemic heart disease[140]. Data from our group demonstrated that HFD intake in mice led to elevated levels of LC3II and p62 in the heart, suggesting the adequate initiation of autophagy with inhibition of autophagosome degradation in obesity[139]. Transmission-electron-microscopy-based assessment of cardiac tissues from mice with HFD-induced obesity revealed the accumulation of double-membraned autophagosomes with an unaltered number of autophagolysosomes compared with mice fed a low-fat diet, consolidating the hypothesis that obesity facilitates the initiation of autophagy and suppresses the degradation of autophagosomes in cardiac tissue. This observation was also associated with decreased expression of RAB7, a small GTPase that governs autophagosome–lysosome fusion[139,141] Further evidence from our study revealed that overactivation of PI3K–AKT signalling is probably responsible for the suppressed degradation of autophagosomes in HFD-induced obesity[139]. Similarly, another group examined cardiac autophagy in a mouse model of obesity exposed to a HFD for 12 weeks[142]. Their data showed that diet-induced obesity increased levels of p62, induced cardiac hypertrophy and preserved fractional shortening in the absence of changes in the ratio of LC3II:LC3I. Additional studies have also suggested a role for both autophagy-mediated proteolytic clearance of cardiac lipoprotein lipase (LPL) and inhibition of autophagy by the pro-inflammatory adaptor protein CARD9 in obesity-related cardiomyopathy[136,137]. These findings infer the existence of suppressed autophagy in the heart during obesity, although interventions to enhance autophagy to ameliorate obesity-associated cardiomyopathy still remain unavailable.

As shown in TABLE 2, suppressed autophagy was observed in animal models of long-term (~20 week) HFD-induced obesity and was associated with decreased phosphorylation of CaM kinase II, inhibitor of NF-κB kinase-β (IKKβ), AMPK, TSC1 and TSC2 as well as increased phosphorylation of mTOR and epigenetic modulator SUV39H[45,79,143–148]. However, increased autophagy and abnormal myocardial architecture were noted in animals with a shorter-term duration (8 week) of HFD feeding[149], in which increased autophagy probably functioned as a compensatory response. In another study using a 24-week high-fat, high-sucrose diet, a key role for autophagy in cardiac health was further supported by the observation that exercise-induced cardiac and metabolic benefits — which were mediated by induction of autophagy via the BCL-2–beclin 1 complex — were diminished with the removal of the stimulus (exercise or starvation)[142]. In addition, the instrumental role for

autophagy in exercise-induced protective effects in the heart is further supported by the observation that cardiac-muscle-specific and skeletal-muscle-specific knockout of *Atg7* exacerbated exercise-induced cardiomyopathy[150]. Moreover, exercise training stimulated unfavourable cardiac remodelling and production of fibroblast growth factor 21 (FGF21), thereby modulating the metabolic phenotype of brown adipose tissue. These results indicate the permissive role for autophagy in exercise-induced beneficial metabolic responses. It should be noted that a deficiency in autophagy proteins is unlikely to elicit any changes in cardiac geometry and function early in life, indicating that insufficient autophagy itself is not innately harmful for metabolic cardiac homeostasis.

Hypertension

Control of blood pressure is crucial for reducing the burden of cardiovascular events in obesity. There are different views regarding the contribution of altered autophagy to endothelial function and peripheral vascular resistance in obesity owing to the discrepancies in animal models, time points and/or autophagic detection methods used in different studies. Zucker obese rats exhibited hypertension and endothelial dysfunction, with impaired AKT–mTOR signalling and excessive autophagy[151]. Treatment of these rats with tetrahydroxystilbene glycoside (TSG) for 2 weeks reactivated the AKT–mTOR pathway and suppressed endothelial autophagy, leading to restoration of blood pressure and endothelial function (FIG. 2d). These TSG-induced beneficial effects were mitigated by treatment with the mTOR inhibitor rapamycin, indicating a role for excessive autophagy in the aetiology of endothelial injury and hypertension[151].

Elevated levels of FFAs, a common phenomenon in obesity and hypertension, were also shown to promote autophagy flux, suppress the proliferation of aortic vascular smooth muscle cells (VSMCs) and alter vascular remodelling, resulting in a loss of VSMCs and interstitial extracellular matrix in vascular walls and, ultimately, the instability of atheromatous plaques[152]. These findings denote the unfavourable effect of excessive autophagy in hypertensive vessels.

With sustained hypertension, left ventricular hypertrophy develops and is accomplished by increases in protein synthesis, the formation of new sarcomeres and remodelling of cellular elements[109,153]. The number of autophagic vacuoles was shown to be markedly reduced within a short time interval after low-dose administration of the β-adrenergic agonist isoprenaline, suggesting that the stimulation of cardiac workload was accompanied by an immediate anticatabolic reaction in rats[154]. Furthermore, suppression of autophagy was noted in pressure-overloaded mouse hearts[155]. Both of these studies revealed that transient suppression of autophagic activity might serve as an early contribution to the adaptive increase in myocardial pressure overload. Nonetheless, the decrease in autophagy might result in the accumulation of harmful proteins and damaged mitochondria, which, in turn, could stimulate the activation of autophagy, suggesting that the initial suppression of autophagy in response to hypertrophy is a transient rather than a durable response.

Nonalcoholic fatty liver disease

NAFLD is closely associated with obesity and insulin resistance[156]. The prevalence of NAFLD is high (20–30%) in Western countries and is associated with a risk of progression to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma[157]. Growing evidence has suggested a role for suppressed autophagy in the aetiology of NAFLD[38,158–162]. Defects in macrophage autophagy (such as *Atg5* knockout) promoted hepatic inflammation and pro-inflammatory M1 macrophage polarization and decreased anti-inflammatory M2 macrophage polarization, leading to the onset of liver injury in mice[96]. Moreover, chronic HFD intake in mice disturbed the formation of autophagolysosomes in the liver[56]. In addition to steatosis, mice with genetically predisposed or HFD-induced obesity exhibited suppressed autophagy (shown as decreased autophagosome formation, lysosomal fusion or lysosome-associated membrane glycoprotein 2 (LAMP2) expression)[68,163–166], leading to unfavourable changes in hepatic functions — including glycogenolysis, gluconeogenesis and β-oxidation — through the turnover of specific cargos regulated by a series of transcription factors[162]. In particular, autophagy stimulates lipid metabolism and offers therapeutic promise for the treatment of NAFLD, alcoholic liver disease, α1-antitrypsin deficiency, hepatocellular carcinoma and viral hepatitis[162].

Treatment with the cholesterol-lowering agent ezetimibe rescued mice from methionine-deficient and choline-deficient diet-induced NASH via AMPK–transcription factor EB (TFEB)-mediated activation of autophagy and inhibition of the NLRP3 inflammasome[167], suggesting a role for AMPK–TFEB-dependent autophagy in steatohepatitis. Clearance of cellular lipid stores via lipophagy is considered an independent route for lipid degradation other than the classic cytosolic lipases[168]. The suppression of autophagy in NAFLD was also explained by the increased levels of rubicon, a beclin 1-interacting negative regulator of autophagosome–lysosome fusion, in NAFLD, which accentuates lipoapoptosis and lipid accumulation while suppressing autophagy[169] (FIG. 2e). Additional evidence has also suggested a possible role for the hepatic lipid droplet-associated protein perilipin (also known as PLIN) family, particularly PLIN2, in the regulation of lipolysis (FIG. 2e). PLIN2 suppresses the association of lipid droplets with cytosolic ATGL and lipophagy proteins, thus leading to decreased lipid oxidation and accumulation of lipid droplets[170]. These findings suggest the therapeutic potential of targeting rubicon and PLIN2 to modulate autophagy in the management of fatty liver disease.

Of note, the regulation of hepatic autophagy might be disrupted in patients with hepatic steatosis. Indeed, a study from our laboratory revealed that knockout of the gene encoding adiponectin (*Adipoq*), an adipose-derived adipokine that is inversely correlated with obesity and NAFLD, reversed HFD-induced hepatic

Lipoapoptosis
Apoptosis caused by exposure to an excess of fatty acids.

injury, apoptosis and suppression of autophagy in mice despite persistent hepatic steatosis[166]. Our data revealed decreased phosphorylation of AKT, signal transducer and activator of transcription 3 (STAT3) and JNK along with increased phosphorylation of AMPK in the liver following HFD intake. Interestingly, *Adipoq* knockout reversed the HFD-induced dephosphorylation of STAT3 and JNK, which probably contributed to the beneficial effect of autophagy. These data suggest that a disparate signalling regulation of autophagy exerts a distinct end point outcome (steatosis, probably associated with AMPK and AKT signalling) and hepatic injury (apoptosis, probably associated with STAT3 and JNK signalling).

Fatty acids are essential to energy metabolism given their role in mitochondrial β-oxidation and ATP generation[171]. Nonetheless, excessive fatty acid flux, which occurs in NAFLD, leads to unfavourable effects on mitochondria if the mitochondrial oxidation capacity is reached. Elevated levels of fatty acids stimulate autophagy to alleviate lipotoxicity[172], which coincides with the enhanced autophagy found at early phases in HFD-induced fatty livers (accumulation of lipids within autophagic vacuoles) followed by the late suppression of autophagy[173]. Levels of triglycerides were increased in hepatocytes after supplementation with fatty acid or exogenous lipids and treatment with autophagy inhibitor 3-methyladenine; however, the rapamycin treatment markedly reduced the number of hepatic lipid droplets by activation of autophagy[55,168,170]. Thus, elevated autophagy as seen in fatty liver disease might serve as a protective mechanism to clear excess lipid droplets and triglycerides in the liver.

The benefit of autophagy induction in NAFLD is also supported by the observation that pharmacological treatment with rapamycin or carbamazepine (an mTOR-independent inducer of autophagy) in HFD-fed mice decreased triglyceride levels in the liver and blood[165,166]. Furthermore, reductions in plasma concentrations of glucose and insulin concentrations were observed, suggesting a beneficial effect of autophagy in NAFLD through both mTOR-dependent or mTOR-independent pathways[174,175]. Additional evidence also supports the concept that a decrease in the number of intracellular lipid droplets occurs in association with a concomitant rise in autophagy flux, thus supporting a role for autophagy in lipolysis (lipophagy)[37,170]. Autophagy might remove lipid droplets in NAFLD and several other fatty liver diseases such as alcohol-induced steatosis[37,176]. Last, but not least, lipid clearance via autophagy is not restricted to the 'lipophagy process' and can occur through other mechanisms involving organelles such as mitochondria and peroxisomes[37,55,170].

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS), an endocrine disorder in women of reproductive age, originates from the dysregulation of the hypothalamic–pituitary–ovarian axis as a result of endocrine and metabolic abnormalities such as hyperandrogenism, central obesity and hyperinsulinaemia[177]. Insulin resistance and obesity are frequently associated with PCOS[177]; however, the mechanisms underlying PCOS are not entirely understood. Downregulated expression of autophagy-related genes has been reported in the endometria of women with PCOS[178]. Elevated insulin levels and/or insulin resistance, which is commonly seen in women with PCOS, impairs ovarian autophagy and function in mice[179]. Consistently, a mouse model of PCOS displayed decreased myocardial autophagy with decreased AMPK activity[180]. In addition, the autophagy activator metformin and caloric restriction have shown beneficial effects in preventing these uterine and cardiac defects in animal models of PCOS[180,181]. Although metformin seems to offer its beneficial effect through the normalization of the androgen-receptor-mediated transcriptional programme and restoration of epithelial–stromal interactions independent of autophagy[181], caloric restriction clearly normalized the suppression of autophagy in PCOS models[180], supporting the therapeutic potential of targeting autophagy in PCOS.

Fetal programming of obesity

Nutritional excess during pregnancy and lactation negatively influences the phenotype of the offspring through a process termed 'fetal programming', possibly owing to changes in substrate availability and utilization[182]. Despite being a fetal and not a maternal organ, the placenta shows an 'obese' phenotype through the inhibition of autophagy in an attempt to adapt to the obesogenic intrauterine environment[183]; inhibition of placental autophagy might predispose offspring to obesity and metabolic diseases through fetal programming. Suppressed autophagy was also found in the liver and hypothalamus in offspring of mothers exposed to a HFD, suggesting a role for altered autophagy in metabolic disturbances in offspring[184]. Further evidence has suggested that oocytes exposed to an obesogenic environment accumulate damaged mitochondria, promoting their oocyte-to-blastocyst transmission owing to defective mitophagy[185].

An altered prenatal nutritional environment influences the genetic regulation of offspring who manifest abnormalities such as cardiac hypertrophy associated with decreased expression of glucose transporter type 4 (GLUT4; also known as SLC2A4) and cardiac fatty acid-binding protein (FABP3) as well as cardiac accumulation of lipids[186,187]. Although the prenatal nutritional environment might alter certain aspects of growth and development per se, the ultimate 'phenotypic end point' is heavily dependent on the postnatal environment (including physical activity, food intake and energy density of food) and obesogenic lifestyle factors, which might influence autophagy[182,186,187].

Targeting autophagy in obesity

Approved clinical interventions for the management of obesity mainly include those aimed at lowering caloric intake or absorption and bariatric surgery (for severe cases of obesity); however, the long-term management of obesity has been difficult. Ample preclinical evidence has accumulated revealing the therapeutic promise of

autophagy modulators for the treatment of obesity and metabolic diseases (TABLE 3). Unfortunately, the clinical efficacy of pharmacological modulation of autophagy has not been proved in obesity.

Pharmacological interventions

Autophagy modulators comprise two distinct categories: mTOR-dependent or mTOR-independent. Although many of the drugs listed in TABLE 3 have been approved by the FDA, the feasibility of modulating autophagy has not been fully validated. Although many drugs that produce beneficial metabolic effects are capable of modulating autophagy, autophagy might not be their only and main mechanism of action. For example, metformin induces GLUT4 translocation and glucose uptake by activation of AMPK, leading to improved clinical outcomes and reduced mortality in individuals with obesity and T2DM[188,189]. However, evidence has described a key role for autophagy induction in the mode of action of metformin[190]. In addition, the thiazolidinedione pioglitazone, an insulin sensitizer that exerts its effects in part by activation of peroxisome proliferator-activated receptor-γ (PPAR-γ), has been shown to promote cytosolic lipolysis, β-oxidation and autophagy and to ameliorate hepatic steatosis[191]. Among the drugs used to decrease caloric intake through appetite suppression, metformin[190], adiponectin[192], leptin[193], the glucagon-like peptide 1 (GLP1) agonists exenatide and liraglutide[194,195], oxyntomodulin (which is probably a GLP1 agonist)[164,196], the amylin receptor agonist pramlintide (AC0137)[197], the neurotransmitter reuptake inhibitor venlafaxine[198], the histamine receptor agonist betahistine[199] and the cannabinoid receptor antagonist rimonabant[200] all possess direct autophagy regulatory properties; however, modulation of autophagy is largely associated with the

Table 3 | **Preclinical studies of autophagy modulators and their metabolic implications**

Compound	Mechanism	Metabolic response	Refs
mTORC1 modulators			
Liraglutide	Decreased mTOR pathway signalling	Reduces glucose levels; improves hepatic lipase activity; decreases hepatic lipid content	164
Pioglitazone	Decreased mTOR pathway signalling	Stimulates adiponectin secretion; increases insulin-stimulated glucose uptake; attenuates left ventricular hypertrophy	237
Ghrelin	Decreased mTOR pathway signalling	Attenuates lipotoxicity and liver fibrosis; inhibits pro-inflammatory response (NF-κB translocation)	238
Rapamycin	mTORC1 inhibitor	Deceases hepatic and blood triglyceride, blood glucose and plasma insulin levels	175
Carbamazepine	mTORC1 inhibitor	Deceases hepatic and blood triglyceride, blood glucose and plasma insulin levels	175
Everolimus	mTORC1 inhibitor	Ameliorates obesity, hypertension, left ventricular hypertrophy and fibrosis and left ventricular diastolic dysfunction; attenuates ROS production and inflammation	239
Proteasome inhibitors			
Bortezomib	Decreased mTOR pathway signalling	Reduces ER stress, inflammation and insulin resistance	240
PI-103	Dual PI3K and AKT inhibitor	Enhances insulin secretion and glycolysis; reduces glucose levels	241
Resveratrol	Decreased AKT1–mTOR pathway signalling	Inhibits glucose uptake; lowers total cholesterol levels and blood pressure; stimulates lipolysis and β-oxidation of fatty acids; reduces inflammation, platelet aggregation and ROS production	242
Quercetin	Decreased AKT1–mTOR pathway signalling	Inhibits intestinal glucose absorption and insulin secretion; improves glucose utilization; alleviates HFD-induced oxidized LDL accumulation	243
Tyrosine kinase inhibitors			
Imatinib	KIT, BCR–ABL and PDGFR inhibitor	Increases ROS production; reduces mitochondrial membrane potential ($\Delta\psi m$) and inhibits oxygen consumption and glycolysis but improves insulin sensitivity and promotes the browning of WAT	201,202
Trastuzumab	Anti-HER2 antibody (inhibition of HER2)	Decreases glucose uptake in cardiomyocytes and downregulates cholesterol-processing genes; increases ROS production	244
Beclin 1 modulators			
Tamoxifen	Oestrogen receptor antagonist and increased *BECN1* expression	Induces perturbations in membrane fluidity; promotes formation of ROS and DNA damage	245
LDL modulators			
Ezetimibe	Cholesterol absorption inhibitor	Inhibits steatohepatitis via AMPK–TFEB-mediated activation of autophagy and inhibition of the NLRP3 inflammasome	167

AKT, protein kinase B; AMPK, AMP-dependent protein kinase; BCR–ABL, breakpoint cluster region–Abelson murine leukaemia; ER, endoplasmic reticulum; HER2, human epidermal growth factor receptor 2 (also known as ERBB2); HFD, high-fat diet; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; NLRP3, NOD-, LRR- and pyrin domain-containing 3; NF-κB, nuclear factor-κB; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; TFEB, transcription factor EB; WAT, white adipose tissue.

suppression of energy intake. Other classic autophagy-promoting compounds such as rapamycin, trehalose and imatinib are also used clinically to improve insulin sensitivity and β-cell function[201,202].

Incretin-based therapies such as dipeptidyl peptidase 4 (DPP-4) inhibitors, which probably have effects on autophagy, have emerged as an important strategy in the treatment of obesity with T2DM[203]. In addition, the sodium/glucose cotransporter 2 (SGLT2; also known as SLC5A2) inhibitor empagliflozin facilitated energy expenditure, ameliorated inflammation and insulin resistance and reduced body weight gain in mice with HFD-induced obesity[204]. Moreover, empagliflozin shifted energy metabolism to favour fat utilization, promoted AMPK and acetyl-CoA carboxylase (ACC) phosphorylation in skeletal muscle and increased hepatic and plasma FGF21 levels[204].

In addition to the therapeutic promise of autophagy induction for the treatment of metabolic anomalies, autophagy inhibition might also offer therapeutic benefit in obesity and related complications. Although GLP1 agonists such as liraglutide might improve metabolic profiles by induction of autophagy[164], a 2017 report revealed that a GLP1 analogue prevented obesity-related glomerulopathy by inhibiting excessive autophagy in podocytes[205]. In addition, thiodigalactoside, a synthetic inhibitor of β-galactoside-binding protein that is used for cancer therapy, promoted browning of WAT and reduced diet-induced adipogenesis, lipogenesis and obesity through inhibition of ATG5 and galectin 1 (REF.[206]). Attainment of WAT browning seems to be a primary mechanism underlying reduction of adiposity in response to autophagy inhibition. Additional evidence has suggested that activation of the PI3K–AKT pathway holds therapeutic potential for the negative regulation of autophagy in obesity, as supported by the observation that HDL and apolipoprotein A-I activated PI3K–AKT–mTORC1 signalling, induced a 'browning' shift in adipocyte phenotype, increased energy expenditure and impeded the development of obesity[207]. Hydroxychloroquine, an antimalarial drug that can inhibit lysosomal function, has also been shown to be beneficial in the treatment of decompensated, treatment-refractory diabetes mellitus and has been shown to reduce the overall risk of diabetes mellitus[208–210].

Lifestyle modification and exercise

In addition to pharmacological interventions, lifestyle modifications such as caloric restriction, weight loss and physical exercise can reverse metabolic inflexibility (that is, a reduced capacity to adjust substrate oxidation on the basis of available substrates), obesity and insulin resistance. Diet restriction and exercise have proven benefits on excess nutrient intake-induced weight gain and obesity-related complications[211,212]. Evidence from our laboratory and others has revealed a pivotal role for autophagy induction in mediating the beneficial effects of diet restriction and exercise in obesity[30,142,211–213]. Caloric restriction and aerobic exercise training facilitate autophagy, enhance peak oxygen consumption and are considered useful physiological stimuli to promote metabolic adaptations that benefit health[214]. A sedentary lifestyle and high-fat, high-caloric food intake are associated with reduced metabolic flexibility, triggering the pathogenesis of obesity, insulin resistance and T2DM[3,7,211,212,215]. Conversely, exercise training and caloric restriction promote autophagy (such as BCL-2-regulated autophagy in exercise)[142], metabolic flexibility and insulin sensitivity in patients with obesity and T2DM[216]. Studies from 2017 have indicated that ketogenic diets promote similar metabolic benefits to that of caloric restriction, including reliance on fatty acid metabolism, production of ketone bodies, resistance to obesity and memory loss and increased lifespan in mice[217,218]. Downregulation of insulin, protein and fatty acid synthesis, upregulation of PPAR-α target gene expression and enhancement of autophagy might contribute to the beneficial effects of ketogenic diets.

Conclusions

A growing body of evidence has revealed the important roles of autophagy in the regulation of adiposity and the development of obesity-related complications (FIG. 2). Although genetic and epigenetic factors are important determinants in the development of obesity, excess caloric intake and decreased physical activity are the main driving forces, promoting altered (suppressed or enhanced) autophagy and impaired systemic metabolism.

Although data from clinical trials evaluating drugs targeting pathophysiological mechanisms in metabolic diseases are still not available, emerging evidence has shown the promise of several compounds that target autophagy for the management of metabolic diseases. However, many challenges still need to be overcome before autophagy-targeted therapeutics will be clinically useful for the management of obesity. First, given the technical difficulties of measuring autophagy activity or flux in humans, most of the knowledge of the role of autophagy in obesity comes from animal studies. Accordingly, clinical translation from multiple preclinical animal studies is challenging owing to contradictory results due to experimental differences. Second, obesity is a complex disorder involving multiple metabolic derangements in insulin sensitivity, glucose and/or lipid metabolism, adipogenesis, sympathetic tone, oxidative stress, apoptosis and mitochondrial integrity. As these metabolic signalling cascades exhibit tissue specificity, the global inhibition or activation of autophagy, or the local modulation at an incorrect time point (for example, upregulated autophagy before the self-repair mechanism is decompensated), might lead to a worsened metabolic condition. Finally, many of the current 'autophagy-targeted' drugs do not directly or specifically modulate autophagy and instead influence upstream pathways leading to alterations in autophagy.

In conclusion, targeting autophagy as a therapeutic strategy for the management of obesity and obesity-related complications has shown promise in preclinical studies. Further studies should focus on the better understanding of the role of altered autophagy in the development of obesity-related diseases, as well as the potential therapeutic utility of pharmacological modulators of autophagy, alone or in combination with lifestyle modification.

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Metabolic inflexibility
Occurs with an inability to adapt fuel oxidation to fuel availability and is characterized by nutrient overload and increased substrate competition, resulting in impaired fuel switching and energy dysregulation.

Ketogenic diets
High-fat, protein-adequate, low-carbohydrate diets that are used primarily to treat difficult-to-control (refractory) epilepsy in children.

1. Bastien, M., Poirier, P., Lemieux, I. & Despres, J. P. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Prog. Cardiovasc. Dis.* **56**, 369–381 (2014).
2. Maiano, C., Hue, O., Morin, A. J. & Moullec, G. Prevalence of overweight and obesity among children and adolescents with intellectual disabilities: a systematic review and meta-analysis. *Obes. Rev.* **17**, 599–611 (2016).
3. Zylke, J. W. & Bauchner, H. The unrelenting challenge of obesity. *JAMA* **315**, 2277–2278 (2016).
4. Flegal, K. M., Kruszon-Moran, D., Carroll, M. D., Fryar, C. D. & Ogden, C. L. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA* **315**, 2284–2291 (2016).
5. Ogden, C. L. et al. Trends in obesity prevalence among children and adolescents in the United States, 1988–1994 through 2013–2014. *JAMA* **315**, 2292–2299 (2016).
6. Curfman, G. D., Morrissey, S. & Drazen, J. M. Sibutramine — another flawed diet pill. *N. Engl. J. Med.* **363**, 972–974 (2010).
7. Vetter, M. L., Faulconbridge, L. F., Webb, V. L. & Wadden, T. A. Behavioral and pharmacologic therapies for obesity. *Nat. Rev. Endocrinol.* **6**, 578–588 (2010).
8. Ochner, C. N., Barrios, D. M., Lee, C. D. & Pi-Sunyer, F. X. Biological mechanisms that promote weight regain following weight loss in obese humans. *Physiol. Behav.* **120**, 106–113 (2013).
9. Afshin, A. et al. Health effects of overweight and obesity in 195 countries over 25 years. *N. Engl. J. Med.* **377**, 13–27 (2017).
10. Jacome-Sosa, M. M. & Parks, E. J. Fatty acid sources and their fluxes as they contribute to plasma triglyceride concentrations and fatty liver in humans. *Curr. Opin. Lipidol.* **25**, 213–220 (2014).
11. Hubler, M. J. & Kennedy, A. J. Role of lipids in the metabolism and activation of immune cells. *J. Nutr. Biochem.* **34**, 1–7 (2016).
12. Ortega, F. B., Lavie, C. J. & Blair, S. N. Obesity and cardiovascular disease. *Circ. Res.* **118**, 1752–1770 (2016).
13. Zhang, Y. & Ren, J. Epigenetics and obesity cardiomyopathy: from pathophysiology to prevention and management. *Pharmacol. Ther.* **161**, 52–66 (2016).
14. Zhang, Y. P., Zhang, Y. Y. & Duan, D. D. From genome-wide association study to phenome-wide association study: new paradigms in obesity research. *Prog. Mol. Biol. Transl Sci.* **140**, 185–231 (2016).
15. Levine, B., Packer, M. & Codogno, P. Development of autophagy inducers in clinical medicine. *J. Clin. Invest.* **125**, 14–24 (2015).
16. Galluzzi, L., Pietrocola, F., Levine, B. & Kroemer, G. Metabolic control of autophagy. *Cell* **159**, 1263–1276 (2014).
17. Choi, A. M., Ryter, S. W. & Levine, B. Autophagy in human health and disease. *N. Engl. J. Med.* **368**, 1845–1846 (2013).
18. Rubinsztein, D. C., Codogno, P. & Levine, B. Autophagy modulation as a potential therapeutic target for diverse diseases. *Nat. Rev. Drug Discov.* **11**, 709–730 (2012).
19. Ignacio-Souza, L. M. et al. Defective regulation of the ubiquitin/proteasome system in the hypothalamus of obese male mice. *Endocrinology* **155**, 2831–2844 (2014).
20. Jaishy, B. et al. Lipid-induced NOX2 activation inhibits autophagic flux by impairing lysosomal enzyme activity. *J. Lipid Res.* **56**, 546–561 (2015).
21. Juarez-Rojas, J. G., Reyes-Soffer, G., Conlon, D. & Ginsberg, H. N. Autophagy and cardiometabolic risk factors. *Rev. Endocr. Metabol. Disord.* **15**, 307–315 (2014).
22. Meng, Q. & Cai, D. Defective hypothalamic autophagy directs the central pathogenesis of obesity via the IκB kinase β (IKKβ)/NF-κB pathway. *J. Biol. Chem.* **286**, 32324–32332 (2011).
23. Kovsan, J. et al. Altered autophagy in human adipose tissues in obesity. *J. Clin. Endocrinol. Metab.* **96**, E268–277 (2011).
24. Jansen, H. J. et al. Autophagy activity is up-regulated in adipose tissue of obese individuals and modulates proinflammatory cytokine expression. *Endocrinology* **153**, 5866–5874 (2012).
25. Kosacka, J. et al. Autophagy in adipose tissue of patients with obesity and type 2 diabetes. *Mol. Cell. Endocrinol.* **409**, 21–32 (2015).
26. Mu, Y. et al. Diet-induced obesity impairs spermatogenesis: a potential role for autophagy. *Sci. Rep.* **7**, 43475 (2017).
27. Yamahara, K. et al. Obesity-mediated autophagy insufficiency exacerbates proteinuria-induced tubulointerstitial lesions. *J. Am. Soc. Nephrol.* **24**, 1769–1781 (2013).
28. Soussi, H., Clement, K. & Dugail, I. Adipose tissue autophagy status in obesity: Expression and flux — two faces of the picture. *Autophagy* **12**, 588–589 (2016).
29. Klionsky, D. J. et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy* **12**, 1–222 (2016).
30. Kim, K. H. & Lee, M. S. Autophagy — a key player in cellular and body metabolism. *Nat. Rev. Endocrinol.* **10**, 322–337 (2014).
31. Lee, H. Y. et al. Autophagy deficiency in myeloid cells increases susceptibility to obesity-induced diabetes and experimental colitis. *Autophagy* **12**, 1390–1403 (2016).
32. Sinha, R. A., Singh, B. K. & Yen, P. M. Reciprocal crosstalk between autophagic and endocrine signaling in metabolic homeostasis. *Endocr. Rev.* **38**, 69–102 (2017).
33. Cheng, Y., Ren, X., Hait, W. N. & Yang, J. M. Therapeutic targeting of autophagy in disease: biology and pharmacology. *Pharmacol. Rev.* **65**, 1162–1197 (2013).
34. Harding, T. M., Morano, K. A., Scott, S. V. & Klionsky, D. J. Isolation and characterization of yeast mutants in the cytoplasm to vacuole protein targeting pathway. *J. Cell Biol.* **131**, 591–602 (1995).
35. Tsukada, M. & Ohsumi, Y. Isolation and characterization of autophagy-defective mutants of *Saccharomyces cerevisiae*. *FEBS Lett.* **333**, 169–174 (1993).
36. Liu, Y. & Levine, B. Autosis and autophagic cell death: the dark side of autophagy. *Cell Death Differ.* **22**, 367–376 (2015).
37. Madrigal-Matute, J. & Cuervo, A. M. Regulation of liver metabolism by autophagy. *Gastroenterology* **150**, 328–339 (2016).
38. Evans, T. D., Sergin, I., Zhang, X. & Razani, B. Target acquired: selective autophagy in cardiometabolic disease. *Sci. Signal.* **10**, eaag2298 (2017).
39. Gatica, D., Lahiri, V. & Klionsky, D. J. Cargo recognition and degradation by selective autophagy. *Nat. Cell Biol.* **20**, 233–242 (2018).
40. Galluzzi, L., Bravo-San Pedro, J. M., Levine, B., Green, D. R. & Kroemer, G. Pharmacological modulation of autophagy: therapeutic potential and persisting obstacles. *Nat. Rev. Drug Discov.* **16**, 487–511 (2017).
41. Lavallard, V. J., Meijer, A. J., Codogno, P. & Gual, P. Autophagy, signaling and obesity. *Pharmacol. Res.* **66**, 513–525 (2012).
42. Botti-Millet, J., Nascimbeni, A. C., Dupont, N., Morel, E. & Codogno, P. Fine-tuning autophagy: from transcriptional to posttranslational regulation. *Am. J. Physiol. Cell Physiol.* **311**, C351–C362 (2016).
43. Nicklin, P. et al. Bidirectional transport of amino acids regulates mTOR and autophagy. *Cell* **136**, 521–534 (2009).
44. Broer, S. & Broer, A. Amino acid homeostasis and signalling in mammalian cells and organisms. *Biochem. J.* **474**, 1935–1963 (2017).
45. Sciarretta, S. et al. Rheb is a critical regulator of autophagy during myocardial ischemia: pathophysiological implications in obesity and metabolic syndrome. *Circulation* **125**, 1134–1146 (2012).
46. Han, J. M. et al. Leucyl-tRNA synthetase is an intracellular leucine sensor for the mTORC1-signaling pathway. *Cell* **149**, 410–424 (2012).
47. Yuan, W. et al. General control nonderepressible 2 (GCN2) kinase inhibits target of rapamycin complex 1 in response to amino acid starvation in *Saccharomyces cerevisiae*. *J. Biol. Chem.* **292**, 2660–2669 (2017).
48. Shimobayashi, M. & Hall, M. N. Multiple amino acid sensing inputs to mTORC1. *Cell Res.* **26**, 7–20 (2016).
49. Meijer, A. J., Lorin, S., Blommaart, E. F. & Codogno, P. Regulation of autophagy by amino acids and MTOR-dependent signal transduction. *Amino Acids* **47**, 2037–2063 (2015).
50. Zhang, F. et al. Branched chain amino acids cause liver injury in obese/diabetic mice by promoting adipocyte lipolysis and inhibiting hepatic autophagy. *EBioMedicine* **13**, 157–167 (2016).
51. Zhou, J. et al. Changes in macroautophagy, chaperone-mediated autophagy, and mitochondrial metabolism in murine skeletal and cardiac muscle during aging. *Aging* **9**, 583–599 (2017).
52. Tan, H. W. S., Sim, A. Y. L. & Long, Y. C. Glutamine metabolism regulates autophagy-dependent mTORC1 reactivation during amino acid starvation. *Nat. Commun.* **8**, 338 (2017).
53. James, H. A., O'Neill, B. T. & Nair, K. S. Insulin regulation of proteostasis and clinical implications. *Cell. Metab.* **26**, 310–323 (2017).
54. Ng, F. & Tang, B. L. Sirtuins' modulation of autophagy. *J. Cell. Physiol.* **228**, 2262–2270 (2013).
55. Wang, K. Molecular mechanism of hepatic steatosis: pathophysiological role of autophagy. *Expert Rev. Mol. Med.* **18**, e14 (2016).
56. Koga, H., Kaushik, S. & Cuervo, A. M. Altered lipid content inhibits autophagic vesicular fusion. *FASEB J.* **24**, 3052–3065 (2010).
57. Engin, A. Non-alcoholic fatty liver disease. *Adv. Exp. Med. Biol.* **960**, 443–467 (2017).
58. Komiya, K. et al. Free fatty acids stimulate autophagy in pancreatic beta-cells via JNK pathway. *Biochem. Biophys. Res. Commun.* **401**, 561–567 (2010).
59. Tan, S. H. et al. Induction of autophagy by palmitic acid via protein kinase C-mediated signaling pathway independent of mTOR (mammalian target of rapamycin). *J. Biol. Chem.* **287**, 14364–14376 (2012).
60. Nguyen, T. B. & Olzmann, J. A. Lipid droplets and lipotoxicity during autophagy. *Autophagy* **13**, 2002–2003 (2017).
61. Cabandugama, P. K., Gardner, M. J. & Sowers, J. R. The renin angiotensin aldosterone system in obesity and hypertension: roles in the cardiorenal metabolic syndrome. *Med. Clin. North Am.* **101**, 129–137 (2017).
62. Oga, E. A. & Eseyin, O. R. The obesity paradox and heart failure: a systematic review of a decade of evidence. *J. Obes.* **2016**, 9040248 (2016).
63. He, C. et al. Beclin 2 functions in autophagy, degradation of G protein-coupled receptors, and metabolism. *Cell* **154**, 1085–1099 (2013).
64. Liu, Y. et al. Bif-1 deficiency impairs lipid homeostasis and causes obesity accompanied by insulin resistance. *Sci. Rep.* **6**, 20453 (2016).
65. Settembre, C. et al. TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop. *Nat. Cell Biol.* **15**, 647–658 (2013).
66. Yasuda-Yamahara, M. et al. Lamp-2 deficiency prevents high-fat diet-induced obese diabetes via enhancing energy expenditure. *Biochem. Biophys. Res. Commun.* **465**, 249–255 (2015).
67. Halban, P. A., Mutkoski, R., Dodson, G. & Orci, L. Resistance of the insulin crystal to lysosomal proteases: implications for pancreatic B cell crinophagy. *Diabetologia* **30**, 348–353 (1987).
68. Yang, L., Li, P., Fu, S., Calay, E. S. & Hotamisligil, G. S. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell. Metab.* **11**, 467–478 (2010).
69. Singh, R. et al. Autophagy regulates adipose mass and differentiation in mice. *J. Clin. Invest.* **119**, 3329–3339 (2009).
70. Zhang, Y. et al. Adipose-specific deletion of autophagy-related gene 7 (atg7) in mice reveals a role in adipogenesis. *Proc. Natl Acad. Sci. USA* **106**, 19860–19865 (2009).
71. Singh, R. et al. Autophagy regulates lipid metabolism. *Nature* **458**, 1131–1135 (2009).
72. Shibata, M. et al. The MAP1-LC3 conjugation system is involved in lipid droplet formation. *Biochem. Biophys. Res. Commun.* **382**, 419–423 (2009).
73. Quan, W. et al. Role of hypothalamic proopiomelanocortin neuron autophagy in the control of appetite and leptin response. *Endocrinology* **153**, 1817–1826 (2012).
74. Lim, Y. M. et al. Systemic autophagy insufficiency compromises adaptation to metabolic stress and facilitates progression from obesity to diabetes. *Nat. Commun.* **5**, 4934 (2014).
75. Houtkooper, R. H., Pirinen, E. & Auwerx, J. Sirtuins as regulators of metabolism and healthspan. *Nat. Rev. Mol. Cell Biol.* **13**, 225–238 (2012).
76. Lapierre, L. R., Kumsta, C., Sandri, M., Ballabio, A. & Hansen, M. Transcriptional and epigenetic regulation of autophagy in aging. *Autophagy* **11**, 867–880 (2015).
77. Mader, B. J. et al. Rotenone inhibits autophagic flux prior to inducing cell death. *ACS Chem. Neurosci.* 3, (1063–1072 (2012).
78. Shin, H. J. et al. AMPK-SKP2-CARM1 signalling cascade in transcriptional regulation of autophagy. *Nature* **534**, 553–557 (2016).

79. Wang, S. et al. ALDH2 protects against high fat diet-induced obesity cardiomyopathy and defective autophagy: role of CaM kinase II, histone H3K9 methyltransferase SUV39H, Sirt1 and PGC-1α deacetylation. *Int. J. Obes*. https://doi.org/10.1038/s41366-018-0030-4 (2018).
80. Mattson, M. P., Longo, V. D. & Harvie, M. Impact of intermittent fasting on health and disease processes. *Ageing Res. Rev.* **39**, 46–58 (2017).
81. Krishan, P., Singh, G. & Bedi, O. Carbohydrate restriction ameliorates nephropathy by reducing oxidative stress and upregulating HIF-1alpha levels in type-1 diabetic rats. *J. Diabetes Metab. Disord.* **16**, 47 (2017).
82. Bellot, G. et al. Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains. *Mol. Cell. Biol.* **29**, 2570–2581 (2009).
83. Alexander, A., Kim, J. & Walker, C. L. ATM engages the TSC2/mTORC1 signaling node to regulate autophagy. *Autophagy* **6**, 672–673 (2010).
84. Scherz-Shouval, R. et al. Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4. *EMBO J.* **26**, 1749–1760 (2007).
85. Madeo, F., Pietrocola, F., Eisenberg, T. & Kroemer, G. Caloric restriction mimetics: towards a molecular definition. *Nat. Rev. Drug Discov.* **13**, 727–740 (2014).
86. Tao, J. et al. Downregulation of Nrf2 promotes autophagy-dependent osteoblastic differentiation of adipose-derived mesenchymal stem cells. *Exp. Cell Res.* **349**, 221–229 (2016).
87. Maixner, N. et al. Transcriptional dysregulation of adipose tissue autophagy in obesity. *Physiology* **31**, 270–282 (2016).
88. Jia, G., Aroor, A. R. & Sowers, J. R. The role of mineralocorticoid receptor signaling in the cross-talk between adipose tissue and the vascular wall. *Cardiovasc. Res.* **113**, 1055–1063 (2017).
89. Shiau, M. Y. et al. Role of PARL-PINK1-Parkin pathway in adipocyte differentiation. *Metabolism* **72**, 1–17 (2017).
90. Mandviwala, T., Khalid, U. & Deswal, A. Obesity and cardiovascular disease: a risk factor or a risk marker? *Curr. Atheroscler. Rep.* **18**, 21 (2016).
91. Haim, Y. et al. Elevated autophagy gene expression in adipose tissue of obese humans: a potential non-cell-cycle-dependent function of E2F1. *Autophagy* **11**, 2074–2088 (2015).
92. Soussi, H. et al. DAPK2 downregulation associates with attenuated adipocyte autophagic clearance in human obesity. *Diabetes* **64**, 3452–3463 (2015).
93. Haim, Y. et al. ASK1 (MAP3K5) is transcriptionally upregulated by E2F1 in adipose tissue in obesity, molecularly defining a human dys-metabolic obese phenotype. *Mol. Metab.* **6**, 725–736 (2017).
94. Slutsky, N. et al. Decreased adiponectin links elevated adipose tissue autophagy with adipocyte endocrine dysfunction in obesity. *Int. J. Obes.* **40**, 912–920 (2016).
95. Mizunoe, Y. et al. Involvement of lysosomal dysfunction in autophagosome accumulation and early pathologies in adipose tissue of obese mice. *Autophagy* **13**, 642–653 (2017).
96. Liu, K. et al. Impaired macrophage autophagy increases the immune response in obese mice by promoting proinflammatory macrophage polarization. *Autophagy* **11**, 271–284 (2015).
97. Xu, X. et al. Obesity activates a program of lysosomal-dependent lipid metabolism in adipose tissue macrophages independently of classic activation. *Cell. Metab.* **18**, 816–830 (2013).
98. Kang, Y. H. et al. Impaired macrophage autophagy induces systemic insulin resistance in obesity. *Oncotarget* **7**, 35577–35591 (2016).
99. Bechor, S. et al. Adipose tissue conditioned media support macrophage lipid-droplet biogenesis by interfering with autophagic flux. *Biochim. Biophys. Acta* **1862**, 1001–1012 (2017).
100. Grijalva, A., Xu, X. & Ferrante, A. W. Jr. Autophagy is dispensable for macrophage-mediated lipid homeostasis in adipose tissue. *Diabetes* **65**, 967–980 (2016).
101. Ouimet, M. et al. Autophagy regulates cholesterol efflux from macrophage foam cells via lysosomal acid lipase. *Cell. Metabolism* **13**, 655–667 (2011).
102. Rambold, A. S., Cohen, S. & Lippincott-Schwartz, J. Fatty acid trafficking in starved cells: regulation by lipid droplet lipolysis, autophagy, and mitochondrial fusion dynamics. *Dev. Cell* **32**, 678–692 (2015).
103. Ye, J. Mechanisms of insulin resistance in obesity. *Front. Med.* **7**, 14–24 (2013).
104. Goginashvili, A. et al. Insulin granules. Insulin secretory granules control autophagy in pancreatic beta cells. *Science* **347**, 878–882 (2015).
105. Yamaguchi, H. et al. Golgi membrane-associated degradation pathway in yeast and mammals. *EMBO J.* **35**, 1991–2007 (2016).
106. Jia, G., DeMarco, V. G. & Sowers, J. R. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. *Nat. Rev. Endocrinol.* **12**, 144–153 (2016).
107. Li, R. et al. 1,25(OH)2 D3 attenuates hepatic steatosis by inducing autophagy in mice. *Obesity* **25**, 561–571 (2017).
108. Song, Y. M. et al. Metformin alleviates hepatosteatosis by restoring SIRT1-mediated autophagy induction via an AMP-activated protein kinase-independent pathway. *Autophagy* **11**, 46–59 (2015).
109. Jia, G., Hill, M. A. & Sowers, J. R. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circ. Res.* **122**, 624–638 (2018).
110. Nishino, I. et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature* **406**, 906–910 (2000).
111. Quan, W. et al. Autophagy deficiency in beta cells leads to compromised unfolded protein response and progression from obesity to diabetes in mice. *Diabetologia* **55**, 392–403 (2012).
112. Ebato, C. et al. Autophagy is important in islet homeostasis and compensatory increase of beta cell mass in response to high-fat diet. *Cell. Metab.* **8**, 325–332 (2008).
113. Jung, H. S. et al. Loss of autophagy diminishes pancreatic beta cell mass and function with resultant hyperglycemia. *Cell. Metab.* **8**, 318–324 (2008).
114. Chang, H. H. et al. Incidence of pancreatic cancer is dramatically increased by a high fat, high calorie diet in KrasG12D mice. *PLoS ONE* **12**, e0184455 (2017).
115. Liu, H. et al. Intermittent fasting preserves beta-cell mass in obesity-induced diabetes via the autophagy-lysosome pathway. *Autophagy* **13**, 1952–1968 (2017).
116. Aoyagi, K. et al. VAMP7 regulates autophagy to maintain mitochondrial homeostasis and to control insulin secretion in pancreatic beta-cells. *Diabetes* **65**, 1648–1659 (2016).
117. Abe, H. et al. Exendin-4 improves beta-cell function in autophagy-deficient beta-cells. *Endocrinology* **154**, 4512–4524 (2013).
118. Chu, K. Y., O'Reilly, L., Ramm, G. & Biden, T. J. High-fat diet increases autophagic flux in pancreatic beta cells in vivo and ex vivo in mice. *Diabetologia* **58**, 2074–2078 (2015).
119. Sun, Q. et al. Factors that affect pancreatic islet cell autophagy in adult rats: evaluation of a calorie-restricted diet and a high-fat diet. *PLoS ONE* **11**, e0151104 (2016).
120. Marsh, B. J. et al. Regulated autophagy controls hormone content in secretory-deficient pancreatic endocrine beta-cells. *Mol. Endocrinol.* **21**, 2255–2269 (2007).
121. Fujitani, Y., Ueno, T. & Watada, H. Autophagy in health and disease. 4. The role of pancreatic beta-cell autophagy in health and diabetes. American journal of physiology. *Cell Physiol.* **299**, C1–C6 (2010).
122. Inoki, K., Kim, J. & Guan, K. L. AMPK and mTOR in cellular energy homeostasis and drug targets. *Annu. Rev. Pharmacol. Toxicol.* **52**, 381–400 (2012).
123. Fujitani, Y., Kawamori, R. & Watada, H. The role of autophagy in pancreatic beta-cell and diabetes. *Autophagy* **5**, 280–282 (2009).
124. Houstis, N., Rosen, E. D. & Lander, E. S. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature* **440**, 944–948 (2006).
125. Petersen, K. F., Dufour, S., Befroy, D., Garcia, R. & Shulman, G. I. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N. Engl. J. Med.* **350**, 664–671 (2004).
126. Alberti, K. G. et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 120, (1640–1645 (2009).
127. Despres, J. P. Abdominal obesity and cardiovascular disease: is inflammation the missing link? *Can. J. Cardiol.* **28**, 642–652 (2012).
128. van Greevenbroek, M. M., Schalkwijk, C. G. & Stehouwer, C. D. Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. *Neth. J. Med.* **71**, 174–187 (2013).
129. Saltiel, A. R. & Olefsky, J. M. Inflammatory mechanisms linking obesity and metabolic disease. *J. Clin. Invest.* **127**, 1–4 (2017).
130. Joven, J., Guirro, M., Marine-Casado, R., Rodriguez-Gallego, E. & Menendez, J. A. Autophagy is an inflammation-related defensive mechanism against disease. *Adv. Exp. Med. Biol.* **824**, 43–59 (2014).
131. Cordero, M. D., Williams, M. R. & Ryffel, B. AMP-activated protein kinase regulation of the NLRP3 inflammasome during aging. *Trends Endocrinol. Metab.* **29**, 8–17 (2018).
132. Cosin-Roger, J. et al. Hypoxia ameliorates intestinal inflammation through NLRP3/mTOR downregulation and autophagy activation. *Nat. Commun.* **8**, 98 (2017).
133. Zhong, Z., Sanchez-Lopez, E. & Karin, M. Autophagy, inflammation, and immunity: a troika governing cancer and its treatment. *Cell* **166**, 288–298 (2016).
134. Lapaquette, P., Guzzo, J., Bretillon, L. & Bringer, M. A. Cellular and molecular connections between autophagy and inflammation. *Mediators Inflamm.* **2015**, 398483 (2015).
135. Jounai, N. et al. NLRP4 negatively regulates autophagic processes through an association with beclin1. *J. Immunol.* **186**, 1646–1655 (2011).
136. Cao, L. et al. CARD9 knockout ameliorates myocardial dysfunction associated with high fat diet-induced obesity. *J. Mol. Cell. Cardiol.* **92**, 185–195 (2016).
137. An, M. et al. ULK1 prevents cardiac dysfunction in obesity through autophagy-meditated regulation of lipid metabolism. *Cardiovasc. Res.* **113**, 1137–1147 (2017).
138. Hu, N. & Zhang, Y. TLR4 knockout attenuated high fat diet-induced cardiac dysfunction via NF-kappaB/JNK-dependent activation of autophagy. *Biochim. Biophys. Acta* **1863**, 2001–2011 (2017).
139. Xu, X., Hua, Y., Nair, S., Zhang, Y. & Ren, J. Akt2 knockout preserves cardiac function in high-fat diet-induced obesity by rescuing cardiac autophagosome maturation. *J. Mol. Cell Biol.* **5**, 61–63 (2013).
140. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* **285**, 2486–2497 (2001).
141. Zhang, Y., Xu, X. & Ren, J. MTOR overactivation and interrupted autophagy flux in obese hearts: a dicey assembly? *Autophagy* **9**, 939–941 (2013).
142. He, C. et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. *Nature* **481**, 511–515 (2012).
143. Li, Z. L. et al. Transition from obesity to metabolic syndrome is associated with altered myocardial autophagy and apoptosis. *Arterioscler. Thromb. Vasc. Biol.* **32**, 1132–1141 (2012).
144. Li, Z. L. et al. Obesity-metabolic derangement exacerbates cardiomyocyte loss distal to moderate coronary artery stenosis in pigs without affecting global cardiac function. *Am. J. Physiol.Heart Circ. Physiol.* **306**, H1087–H1101 (2014).
145. Xu, X. & Ren, J. Macrophage migration inhibitory factor (MIF) knockout preserves cardiac homeostasis through alleviating Akt-mediated myocardial autophagy suppression in high-fat diet-induced obesity. *Int. J. Obes.* **39**, 387–396 (2015).
146. Kandadi, M. R. et al. Deletion of protein tyrosine phosphatase 1B rescues against myocardial anomalies in high fat diet-induced obesity: role of AMPK-dependent autophagy. *Biochim. Biophys. Acta* **1852**, 299–309 (2015).
147. Liang, L. et al. Antioxidant catalase rescues against high fat diet-induced cardiac dysfunction via an IKKbeta-AMPK-dependent regulation of autophagy. *Biochim. Biophys. Acta* **1852**, 343–352 (2015).
148. Guo, R., Zhang, Y., Turdi, S. & Ren, J. Adiponectin knockout accentuates high fat diet-induced obesity and cardiac dysfunction: role of autophagy. *Biochim. Biophys. Acta* **1832**, 1136–1148 (2013).
149. Lai, C. H. et al. Multi-strain probiotics inhibit cardiac myopathies and autophagy to prevent heart injury in high-fat diet-fed rats. *Int. J. Med. Sci.* **13**, 277–285 (2016).
150. Yan, Z. et al. Exercise leads to unfavourable cardiac remodelling and enhanced metabolic homeostasis in obese mice with cardiac and skeletal muscle autophagy deficiency. *Sci. Rep.* **7**, 7894 (2017).
151. Dong, Q. et al. Tetrahydroxystilbene glycoside improves microvascular endothelial dysfunction and

ameliorates obesity-associated hypertension in obese ZDF rats via inhibition of endothelial autophagy. *Cell. Physiol. Biochem.* **43**, 293–307 (2017).
152. Cheng, C. I. et al. Free fatty acids induce autophagy and LOX-1 upregulation in cultured aortic vascular smooth muscle cells. *J. Cell. Biochem.* **118**, 1249–1261 (2017).
153. Messerli, F. H., Rimoldi, S. F. & Bangalore, S. The transition from hypertension to heart failure: contemporary update. *JACC Heart Fail.* **5**, 543–551 (2017).
154. Pfeifer, U., Föhr, J., Wilhelm, W. & Dämmrich, J. Short-term inhibition of cardiac cellular autophagy by isoproterenol. *J. Mol. Cell. Cardiol.* **19**, 1179–1184 (1987).
155. Shirakabe, A. et al. Drp1-dependent mitochondrial autophagy plays a protective role against pressure overload-induced mitochondrial dysfunction and heart failure. *Circulation* **133**, 1249–1263 (2016).
156. De Meyer, G. R. et al. Autophagy in vascular disease. *Circ. Res.* **116**, 468–479 (2015).
157. Nielsen, J. Systems biology of metabolism: a driver for developing personalized and precision medicine. *Cell. Metab.* **25**, 572–579 (2017).
158. Yu, W. et al. Sirt3 deficiency exacerbates diabetic cardiac dysfunction: Role of Foxo3A-Parkin-mediated mitophagy. *Biochim. Biophys. Acta* **1863**, 1973–1983 (2017).
159. Negri, T. et al. Chromosome band 17q21 in breast cancer: significant association between beclin 1 loss and HER2/NEU amplification. *Genes Chromosomes Cancer* **49**, 901–909 (2010).
160. Li, S. et al. SIRT3 acts as a negative regulator of autophagy dictating hepatocyte susceptibility to lipotoxicity. *Hepatology* **66**, 936–952 (2017).
161. Shen, C. et al. Nicotinamide protects hepatocytes against palmitate-induced lipotoxicity via SIRT1-dependent autophagy induction. *Nutr. Res.* **40**, 40–47 (2017).
162. Ueno, T. & Komatsu, M. Autophagy in the liver: functions in health and disease. *Nat. Rev. Gastroenterol. Hepatol.* **14**, 170–184 (2017).
163. Aijala, M. et al. Long-term fructose feeding changes the expression of leptin receptors and autophagy genes in the adipose tissue and liver of male rats: a possible link to elevated triglycerides. *Genes Nutr.* **8**, 623–635 (2013).
164. He, Q., Sha, S., Sun, L., Zhang, J. & Dong, M. GLP-1 analogue improves hepatic lipid accumulation by inducing autophagy via AMPK/mTOR pathway. *Biochem. Biophys. Res. Commun.* **476**, 196–203 (2016).
165. Chang, E. et al. Ezetimibe improves hepatic steatosis in relation to autophagy in obese and diabetic rats. *World J. Gastroenterol.* **21**, 7754–7763 (2015).
166. Guo, R., Nair, S., Zhang, Y. & Ren, J. Adiponectin deficiency rescues high-fat diet-induced hepatic injury, apoptosis and autophagy loss despite persistent steatosis. *Int. J. Obes.* **41**, 1403–1412 (2017).
167. Kim, S. H. et al. Ezetimibe ameliorates steatohepatitis via AMP activated protein kinase-TFEB-mediated activation of autophagy and NLRP3 inflammasome inhibition. *Autophagy* **13**, 1767–1781 (2017).
168. Liu, J. & Debnath, J. The evolving, multifaceted roles of autophagy in cancer. *Adv. Cancer Res.* **130**, 1–53 (2016).
169. Tanaka, S. et al. Rubicon inhibits autophagy and accelerates hepatocyte apoptosis and lipid accumulation in nonalcoholic fatty liver disease in mice. *Hepatology* **64**, 1994–2014 (2016).
170. Kaushik, S. & Cuervo, A. M. Degradation of lipid droplet-associated proteins by chaperone-mediated autophagy facilitates lipolysis. *Nat. Cell Biol.* **17**, 759–770 (2015).
171. Martinez-Vicente, M. Neuronal Mitophagy in neurodegenerative diseases. *Front. Mol. Neurosci.* **10**, 64 (2017).
172. Chen, Y., Xu, C., Yan, T., Yu, C. & Li, Y. Omega-3 fatty acids reverse lipotoxity through induction of autophagy in nonalcoholic fatty liver disease. *Nutrition* **31**, 1423–1429.e2 (2015).
173. Hsu, H. C. et al. Time-dependent cellular response in the liver and heart in a dietary-induced obese mouse model: the potential role of ER stress and autophagy. *Eur. J. Nutr.* **55**, 2031–2043 (2016).
174. Mao, Y., Yu, F., Wang, J., Guo, C. & Fan, X. Autophagy: a new target for nonalcoholic fatty liver disease therapy. *Hepat. Med.* **8**, 27–37 (2016).
175. Lin, C. W. et al. Pharmacological promotion of autophagy alleviates steatosis and injury in alcoholic and non-alcoholic fatty liver conditions in mice. *J. Hepatol.* **58**, 993–999 (2013).
176. Guo, R., Xu, X., Babcock, S. A., Zhang, Y. & Ren, J. Aldehyde dedydrogenase-2 plays a beneficial role in ameliorating chronic alcohol-induced hepatic steatosis and inflammation through regulation of autophagy. *J. Hepatol.* **62**, 647–656 (2015).
177. Bani Mohammad, M. & Majdi Seghinsara, A. Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH. *Asian Pac. J. Cancer Prev.* **18**, 17–21 (2017).
178. Sumarac-Dumanovic, M. et al. Downregulation of autophagy gene expression in endometria from women with polycystic ovary syndrome. *Mol. Cell. Endocrinol.* **440**, 116–124 (2017).
179. Su, Y. et al. High insulin impaired ovarian function in early pregnant mice and the role of autophagy in this process. *Endocr. J.* **64**, 613–621 (2017).
180. Gao, L. et al. Calcitriol attenuates cardiac remodeling and dysfunction in a murine model of polycystic ovary syndrome. *Endocrine* **52**, 363–373 (2016).
181. Zhang, Y. et al. Metformin ameliorates uterine defects in a rat model of polycystic ovary syndrome. *EBioMedicine* **18**, 157–170 (2017).
182. Dong, M., Zheng, Q., Ford, S. P., Nathanielsz, P. W. & Ren, J. Maternal obesity, lipotoxicity and cardiovascular diseases in offspring. *J. Mol. Cell. Cardiol.* **55**, 111–116 (2013).
183. Muralimanoharan, S., Gao, X., Weintraub, S., Myatt, L. & Maloyan, A. Sexual dimorphism in activation of placental autophagy in obese women with evidence for fetal programming from a placenta-specific mouse model. *Autophagy* **12**, 752–769 (2016).
184. Reginato, A. et al. Autophagy proteins are modulated in the liver and hypothalamus of the offspring of mice with diet-induced obesity. *J. Nutr. Biochem.* **34**, 30–41 (2016).
185. Boudoures, A. L. et al. Obesity-exposed oocytes accumulate and transmit damaged mitochondria due to an inability to activate mitophagy. *Dev. Biol.* **426**, 126–138 (2017).
186. Navarro, E., Funtikova, A. N., Fito, M. & Schroder, H. Prenatal nutrition and the risk of adult obesity: long-term effects of nutrition on epigenetic mechanisms regulating gene expression. *J. Nutr. Biochem.* **39**, 1–14 (2017).
187. Zhu, S., Eclarinal, J., Baker, M. S., Li, G. & Waterland, R. A. Developmental programming of energy balance regulation: is physical activity more 'programmable' than food intake? *Proc. Nutr. Soc.* **75**, 73–77 (2016).
188. Wong, A. K. et al. The effect of metformin on insulin resistance and exercise parameters in patients with heart failure. *Eur. J. Heart Fail.* **14**, 1303–1310 (2012).
189. Jia, G., Jia, Y. & Sowers, J. R. Contribution of maladaptive adipose tissue expansion to development of cardiovascular disease. *Compr. Physiol.* **7**, 253–262 (2016).
190. Jiang, Y. et al. Metformin plays a dual role in MIN6 pancreatic beta cell function through AMPK-dependent autophagy. *Int. J. Biol. Sci.* **10**, 268–277 (2014).
191. Hsiao, P. J. et al. Pioglitazone enhances cytosolic lipolysis, beta-oxidation and autophagy to ameliorate hepatic steatosis. *Sci. Rep.* **7**, 9030 (2017).
192. Liu, Y. et al. Adiponectin stimulates autophagy and reduces oxidative stress to enhance insulin sensitivity during high-fat diet feeding in mice. *Diabetes* **64**, 36–48 (2015).
193. Hussain, Z. & Khan, J. A. Food intake regulation by leptin: mechanisms mediating gluconeogenesis and energy expenditure. *Asian Pac. J. Trop. Med.* **10**, 940–944 (2017).
194. Sun, F. et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss in patients with type 2 diabetes: a systematic review and network meta-analysis. *J. Diabetes Res.* **2015**, 157201 (2015).
195. Tomlinson, B., Hu, M., Zhang, Y., Chan, P. & Liu, Z. M. Investigational glucagon-like peptide-1 agonists for the treatment of obesity. *Expert Opin. Invest. Drugs* **25**, 1167–1179 (2016).
196. Sharma, S., Mells, J. E., Fu, P. P., Saxena, N. K. & Anania, F. A. GLP-1 analogs reduce hepatocyte steatosis and improve survival by enhancing the unfolded protein response and promoting macroautophagy. *PLoS ONE* **6**, e25269 (2011).
197. Venkatanarayan, A. et al. IAPP-driven metabolic reprogramming induces regression of p53-deficient tumours in vivo. *Nature* **517**, 626–630 (2015).
198. Alcocer-Gomez, E. et al. Antidepressants induce autophagy dependent-NLRP3-inflammasome inhibition in major depressive disorder. *Pharmacol. Res.* **121**, 114–121 (2017).
199. Morissette, G., Lodge, R., Bouthillier, J. & Marceau, F. Receptor-independent, vacuolar ATPase-mediated cellular uptake of histamine receptor-1 ligands: possible origin of pharmacological distortions and side effects. *Toxicol. Appl. Pharmacol.* **229**, 320–331 (2008).
200. Hiebel, C., Kromm, T., Stark, M. & Behl, C. Cannabinoid receptor 1 modulates the autophagic flux independent of mTOR- and BECLIN1-complex. *J. Neurochem.* **131**, 484–497 (2014).
201. Choi, S. S. et al. PPARgamma antagonist gleevec improves insulin sensitivity and promotes the browning of white adipose tissue. *Diabetes* **65**, 829–839 (2016).
202. Paech, F., Bouitbir, J. & Krahenbuhl, S. Hepatocellular toxicity associated with tyrosine kinase inhibitors: mitochondrial damage and inhibition of glycolysis. *Front. Pharmacol.* **8**, 367 (2017).
203. Courtney, H., Nayar, R., Rajeswaran, C. & Jandhyala, R. Long-term management of type 2 diabetes with glucagon-like peptide-1 receptor agonists. *Diabetes Metab. Syndr. Obes.* **10**, 79–87 (2017).
204. Xu, L. et al. SGLT2 inhibition by empagliflozin promotes fat utilization and browning and attenuates inflammation and insulin resistance by polarizing M2 macrophages in diet-induced obese mice. *EBioMedicine* **20**, 137–149 (2017).
205. Guo, H. et al. Glucagon-like peptide-1 analog prevents obesity-related glomerulopathy by inhibiting excessive autophagy in podocytes. *Am. J. Physiol. Renal Physiol.* **314**, F181–F189 (2018).
206. Parray, H. A. & Yun, J. W. Combined inhibition of autophagy protein 5 and galectin-1 by thiodigalactoside reduces diet-induced obesity through induction of white fat browning. *IUBMB Life* **69**, 510–521 (2017).
207. Wang, S. & Peng, D. Regulation of adipocyte autophagy — the potential anti-obesity mechanism of high density lipoprotein and ApolipoproteinA-I. *Lipids Health Dis.* **11**, 131 (2012).
208. Quatraro, A. et al. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? *Ann. Intern. Med.* **112**, 678–681 (1990).
209. Gerstein, H. C., Thorpe, K. E., Taylor, D. W. & Haynes, R. B. The effectiveness of hydroxychloroquine in patients with type 2 diabetes mellitus who are refractory to sulfonylureas — a randomized trial. *Diabetes Res. Clin. Pract.* **55**, 209–219 (2002).
210. Wasko, M. C. et al. Antidiabetogenic effects of hydroxychloroquine on insulin sensitivity and beta cell function: a randomised trial. *Diabetologia* **58**, 2336–2343 (2015).
211. Alrushud, A. S., Rushton, A. B., Kanavaki, A. M. & Greig, C. A. Effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese older adults with knee osteoarthritis: a systematic review and mixed method data synthesis. *BMJ Open* **7**, e014537 (2017).
212. Webb, V. L. & Wadden, T. A. Intensive lifestyle intervention for obesity: principles, practices, and results. *Gastroenterology* **152**, 1752–1764 (2017).
213. Han, X. et al. Influence of long-term caloric restriction on myocardial and cardiomyocyte contractile function and autophagy in mice. *J. Nutr. Biochem.* **23**, 1592–1599 (2012).
214. Kitzman, D. W. et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* **315**, 36–46 (2016).
215. Ludwig, D. S. Lifespan weighed down by diet. *JAMA* **315**, 2269–2270 (2016).
216. Halling, J. F. & Pilegaard, H. Autophagy-dependent beneficial effects of exercise. *Cold Spring Harb. Perspect. Med.* **7**, a029777 (2017).
217. Newman, J. C. et al. Ketogenic diet reduces midlife mortality and improves memory in aging mice. *Cell. Metab.* **26**, 547–557.e8 (2017).
218. Roberts, M. N. et al. A ketogenic diet extends longevity and healthspan in adult mice. *Cell. Metab.* **26**, 539–546 e5 (2017).
219. Pyo, J. O. et al. Overexpression of Atg5 in mice activates autophagy and extends lifespan. *Nat. Commun.* **4**, 2300 (2013).
220. Ma, D. et al. Autophagy deficiency by hepatic FIP200 deletion uncouples steatosis from liver injury in NAFLD. *Mol. Endocrinol.* **27**, 1643–1654 (2013).
221. Jaber, N. et al. Class III PI3K Vps34 plays an essential role in autophagy and in heart and liver function. *Proc. Natl Acad. Sci. USA* **109**, 2003–2008 (2012).

222. Kim, K. H. et al. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing Fgf21 as a mitokine. *Nat. Med.* **19**, 83–92 (2013).
223. Shigihara, N. et al. Human IAPP-induced pancreatic beta cell toxicity and its regulation by autophagy. *J. Clin. Invest.* **124**, 3634–3644 (2014).
224. Fernandez, A. F. et al. Autophagy couteracts weight gain, lipotoxicity and pancreatic beta-cell death upon hypercaloric pro-diabetic regimens. *Cell Death Dis.* **8**, e2970 (2017).
225. Liu, L., Liu, J. & Yu, X. Dipeptidyl peptidase-4 inhibitor MK-626 restores insulin secretion through enhancing autophagy in high fat diet-induced mice. *Biochem. Biophys. Res. Commun.* **470**, 516–520 (2016).
226. Gao, X., Yan, D., Zhao, Y., Tao, H. & Zhou, Y. Moderate calorie restriction to achieve normal weight reverses beta-cell dysfunction in diet-induced obese mice: involvement of autophagy. *Nutr. Metab.* **12**, 34 (2015).
227. Soeda, J. et al. Maternal obesity alters endoplasmic reticulum homeostasis in offspring pancreas. *J. Physiol. Biochem.* **72**, 281–291 (2016).
228. Lopez-Vicario, C. et al. Inhibition of soluble epoxide hydrolase modulates inflammation and autophagy in obese adipose tissue and liver: role for omega-3 epoxides. *Proc. Natl Acad. Sci. USA* **112**, 536–541 (2015).
229. He, B., Liu, L., Yu, C., Wang, Y. & Han, P. Roux-en-Y gastric bypass reduces lipid overaccumulation in liver by upregulating hepatic autophagy in obese diabetic rats. *Obes. Surg.* **25**, 109–118 (2015).
230. Rodriguez-Navarro, J. A. et al. Inhibitory effect of dietary lipids on chaperone-mediated autophagy. *Proc. Natl Acad. Sci. USA* **109**, E705–E714 (2012).
231. Liu, H. Y. et al. Hepatic autophagy is suppressed in the presence of insulin resistance and hyperinsulinemia: inhibition of FoxO1-dependent expression of key autophagy genes by insulin. *J. Biol. Chem.* **284**, 31484–31492 (2009).
232. Inami, Y. et al. Hepatic steatosis inhibits autophagic proteolysis via impairment of autophagosomal acidification and cathepsin expression. *Biochem. Biophys. Res. Commun.* **412**, 618–625 (2011).
233. Parafati, M. et al. Bergamot polyphenol fraction prevents nonalcoholic fatty liver disease via stimulation of lipophagy in cafeteria diet-induced rat model of metabolic syndrome. *J. Nutr. Biochem.* **26**, 938–948 (2015).
234. Xiao, J. et al. Lycium barbarum polysaccharides therapeutically improve hepatic functions in non-alcoholic steatohepatitis rats and cellular steatosis model. *Sci. Rep.* **4**, 5587 (2014).
235. Yan, H., Gao, Y. & Zhang, Y. Inhibition of JNK suppresses autophagy and attenuates insulin resistance in a rat model of nonalcoholic fatty liver disease. *Mol. Med. Rep.* **15**, 180–186 (2017).
236. Xu, Q. et al. Adipose tissue autophagy related gene expression is associated with glucometabolic status in human obesity. *Adipocyte* https://doi.org/10.1080/21623945.2017.1394537 (2018).
237. Matsuura, N. et al. Effects of pioglitazone on cardiac and adipose tissue pathology in rats with metabolic syndrome. *Int. J. Cardiol.* **179**, 360–369 (2015).
238. Mao, Y. et al. Ghrelin attenuated lipotoxicity via autophagy induction and nuclear factor-kappaB inhibition. *Cell. Physiol. Biochem.* **37**, 563–576 (2015).
239. Uchinaka, A., Yoneda, M., Yamada, Y., Murohara, T. & Nagata, K. Effects of mTOR inhibition on cardiac and adipose tissue pathology and glucose metabolism in rats with metabolic syndrome. *Pharmacol. Res. Perspect.* **5**, e00331 (2017).
240. Kwak, H. J. et al. Bortezomib attenuates palmitic acid-induced ER stress, inflammation and insulin resistance in myotubes via AMPK dependent mechanism. *Cell. Signal.* **28**, 788–797 (2016).
241. Bhattacharya, B. et al. Increased drug resistance is associated with reduced glucose levels and an enhanced glycolysis phenotype. *Br. J. Pharmacol.* **171**, 3255–3267 (2014).
242. Borriello, A. et al. Resveratrol: from basic studies to bedside. *Cancer Treat. Res.* **159**, 167–184 (2014).
243. Liu, L., Gao, C., Yao, P. & Gong, Z. Quercetin alleviates high-fat diet-induced oxidized low-density lipoprotein accumulation in the liver: implication for autophagy regulation. *BioMed Res. Int.* **2015**, 607531 (2015).
244. Necela, B. M. et al. The antineoplastic drug, trastuzumab, dysregulates metabolism in iPSC-derived cardiomyocytes. *Clin. Transl Med.* **6**, 5 (2017).
245. Bursch, W. et al. Cell death and autophagy: cytokines, drugs, and nutritional factors. *Toxicology* **254**, 147–157 (2008).

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