Molecules and Cells

Minireview

Autophagy Dysregulation and Obesity-Associated Pathologies

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http://dx.doi.org/10.14348/molcells.2018.2213
www.molcells.org

Autophagy is one of the major degradative mechanisms that can eliminate excessive nutrients, toxic protein aggregates, damaged organelles and invading microorganisms. In response to obesity and obesity-associated lipotoxic, proteotoxic and oxidative stresses, autophagy plays an essential role in maintaining physiological homeostasis. However, obesity and its associated stress insults can often interfere with the autophagic process through various mechanisms, which result in further aggravation of obesity-related metabolic pathologies in multiple metabolic organs. Paradoxically, inhibition of autophagy, within specific contexts, indirectly produces beneficial effects that can alleviate several detrimental consequences of obesity. In this minireview, we will provide a brief discussion about our current understanding of the impact of obesity on autophagy and the role of autophagy dysregulation in modulating obesity-associated pathological outcomes.

Keywords: autophagy, diabetes, metabolism, obesity, stress

INTRODUCTION

As highlighted by the 2016 Nobel Prize in Physiology or Medicine, autophagy is now considered the major mechanism through which cells remove unnecessary or toxic cellular constituents (Tooze and Dikic, 2016). The process of autophagy and its critical role in physiological homeostasis have been extensively reviewed in recent literature (Choi et al., 2013; Feng et al., 2014; Kaur and Debnath, 2015), so will be only briefly summarized in this introduction.

Initial genetic screens in yeast identified autophagy-regulating genetic components, now catalogued as ATG genes (Feng et al., 2014; Klionsky et al., 2003). ATG genes constitute the pathways that lead to the formation of the isolation membrane, which sequesters target substrates from the cytoplasm through autophagosome formation (Feng et al., 2014). Mature autophagosomes then fuse with lysosomes, which contain digestive enzymes, to form autolysosomes, in which the substrates are degraded and the simple molecules are released for recycling through lysosomal channels. Although many key genetic components of autophagy have been characterized, further investigations are still necessary to understand how each step of autophagy is mechanistically mediated by its biochemical components (Feng et al., 2014).

The physiological importance of autophagy has been clearly demonstrated by genetic studies in model animals such as mice and Drosophila (Mizushima and Levine, 2010; Mulakkal et al., 2014). For instance, autophagy defects in neurons provoke neurodegenerative phenotypes associated with toxic protein aggregates (Kim et al., 2017; Menzies et al., 2017). These aggregates are often observed in human patients with neurodegenerative diseases (Ross and Poirier, 2004). In addition, autophagy defects also generate prominent phenotypes in metabolic organs, such as liver, adipose tissue, skeletal muscle and pancreas (Kim and Lee, 2014). These studies indicate that autophagy indeed plays an important catabolic role and that proper regulation of autophagy is important for metabolic homeostasis.

Received 5 September, 2017; revised 2 October, 2017; accepted 10 October, 2017; published online 23 January, 2018

eISSN: 0219-1032

Obesity, which affects up to 2.1 billion people or ~30% of the population worldwide (Ng et al., 2014), is now a global health concern. Obesity is frequently associated with its diverse comorbidities such as diabetes, hypertension, dyslipidemia, cardiovascular disease and cancer (Collaborators et al., 2017; Kopelman, 2000). As autophagy may play a critical role in preventing or attenuating these diseases, recent studies have focused on how the autophagy process is altered during obesity and how autophagic catabolism plays a role in preventing the comorbidities of obesity.

OBESITY-ASSOCIATED STRESS INSULTS

Over-nutrition and lack of physical activity, prevalent in modern society, are among the major causes of the current obesity epidemic (Hill et al., 2003; 2012; Stubbs and Lee, 2004). These conditions lead to a chronic surplus of calories, which is stored as fat in adipose tissue. Accumulation of fat in non-adipose tissue, such as liver and skeletal muscle, can provoke tissue damage (Brookheart et al., 2009; Lelliott and Vidal-Puig, 2004). In addition, excessive fat accumulation can elevate serum free fatty acid level, resulting in systemic lipotoxicity (Browning and Horton, 2004; Brookheart et al., 2009; Goldberg et al., 2012; Lelliott and Vidal-Puig, 2004).

Lipid is the major constituent of the biological membrane, and excessive lipid influx and accumulation of byproducts from lipid metabolism can alter cellular processes by affecting membrane integrity and fluidity. For instance, sarco-ER calcium pump (SERCA) activity requires a fluidic ER membrane and is inhibited by saturated fatty acids and cholesterol that rigidify the membrane (Li et al., 2004) or even by obesity-associated moderate changes in ER membrane lipidomic profile (Fu et al., 2011). SERCA inhibition and subsequent reduction in ER calcium level can lead to a decreased activity of calcium-dependent ER chaperones, resulting in decreased protein folding capacity and subsequent accumulation of unfolded proteins (Arruda and Hotamisligil, 2015; Ji and Kaplowitz, 2006). Furthermore, unfolded protein accumulation induces proteotoxic stresses in the ER (ER stress), which can promote lipogenesis (Basseri and Austin, 2008; Zheng et al., 2010) and interfere with the normal lipoprotein secretion pathway (Ota et al., 2008; Zhang et al., 2011). These outcomes can further aggravate lipotoxic pathologies. Accumulation of cytotoxic lipids also provokes oxidative stress, as the reactive lipids damage critical biomolecules such as membrane-bound mitochondrial enzymes (Hauck and Bernlohr, 2016). The oxidative stress can be further propagated by mitochondrial damages that lead to production of reactive oxygen species (ROS) (Bournat and Brown, 2010). Excessive oxidative damage in DNA, in turn, can also produce genotoxic stresses (Cerda et al., 2014; Cooke et al., 2003). Membrane lipid alteration can also provoke stress signaling through modification of lipid subdomains known as lipid rafts, and induce stress-activated protein kinase (SAPK)/JNK signaling that aggravates obesity-associated metabolic pathologies (Holzer et al., 2011). In addition, extracellular fatty acids are directly sensed by toll-like receptors to elicit stress responses (Kennedy et al., 2009; Shi et al., 2006), and various metabolites of fatty acids indirectly provoke activation of stress signaling pathways (Schenk et al., 2008). These responses collectively lead to an aggravation of obesity-associated pathologies, such as chronic inflammation and insulin resistance (Kennedy et al., 2009; Schenk et al., 2008).

Autophagy plays an important protective role against these stress insults (Kroemer et al., 2010; Murrow and Debnath, 2013). For example, elimination of lipid droplets through the autophagic pathway (known as lipophagy) provides a mechanism for reducing fat content and thereby normalizing lipid metabolism in tissues of obese individuals (Singh and Cuervo, 2012; Singh et al., 2009a). Autophagy can also remove dysfunctional mitochondria (known as mitophagy), limiting production of ROS in obesity-associated pathological conditions (Sarparanta et al., 2017). During ER stress, autophagy can eliminate a portion of the ER (known as ER-phagy), which removes damaged or redundant parts of the ER restoring ER homeostasis (Bernales et al., 2007). Therefore, to resolve the obesity-associated stresses, autophagic responses should be properly coordinated; however, these stresses can often impair autophagic processes, as highlighted below.

IMPACT OF OBESITY ON AUTOPHAGY

ATG1 is one of the first genes isolated to mediate the autophagy response in yeast (Kamada et al., 2000; Matsuura et al., 1997). Unc-51-like kinase 1 (ULK1) and 2 (ULK2), ATG1's mammalian homologs, are essential for initiation of autophagy (Alers et al., 2012a). Activity of ULK1 is controlled by two nutrient-regulated protein kinases, AMP-activated kinase (AMPK) and mTOR complex 1 (mTORC1) (Alers et al., 2012b). AMPK is activated upon cellular energy (ATP) depletion while mTORC1 is activated upon nutrient abundance (Jewell and Guan, 2013). AMPK is known to inhibit mTORC1 through several distinct mechanisms (Jewell and Guan, 2013). AMPK and mTORC1 produce diametrically opposing effects on ULK1; ULK1 is activated by AMPK-mediated phosphorylation but inhibited by mTORC1-mediated phosphorylation. Through these mechanisms, autophagy can be activated by starvation while suppressed during nutritional affluence (Galluzzi et al., 2014). Indeed, hepatic autophagy is strongly upregulated during starvation and coordinates liver metabolism to meet the metabolic needs of the organism during the nutritional stringency (Ezaki et al., 2011).

Autophagy was thought to be inactive during obesity because hypernutrition can inhibit AMPK and subsequently activate mTORC1. Indeed, mTORC1 activity is chronically upregulated during obesity, which is associated with increased anabolic metabolism in liver (Dann et al., 2007; Um et al., 2004). Consistent with this premise, initial studies on obese mice showed dramatic downregulation of autophagic activities, associated with reduced expression of ATG5 and ATG7 and the subsequent inhibition in autophagosome biogenesis (Yang et al., 2010). Insulin resistance and hyperinsulinemia were also suggested to contribute to autophagy inhibition during obesity (Liu et al., 2009). In addition, recent studies suggest that lipotoxic insults can downregulate

AMPK signaling, thereby decreasing autophagosome production in macrophages (Wen et al., 2011) and liver cells (Cho et al., 2017; Li et al., 2017).

In contrast, other studies involving both human and mouse tissues demonstrated that autophagosomes can accumulate in response to obesity and lipotoxicity in multiple tissues, including liver and adipose tissues (Jansen et al., 2012; Kovsan et al., 2011; Mei et al., 2011; Nunez et al., 2013; Ost et al., 2010). These findings suggest that the relationship between obesity and autophagy is not as simple as originally speculated. For instance, ER stress, which can be provoked by obesity and lipotoxicity as reviewed above, can induce autophagy through multiple mechanisms (Ogata et al., 2006; Qin et al., 2010; Rashid et al., 2015; Senft and Ronai, 2015). Obesity *per se* is an established strong inducer of ER stress in liver (Hotamisligil, 2010; Ozcan et al., 2004) and obesity-associated ER stress aggravates fat accumulation, insulin resistance and liver damage (Ozcan et al., 2006; Park et al., 2014a). Therefore, it is plausible that, as a defensive mechanism against ER stress-induced damages, cells upregulate autophagy. In fibroblasts, lipotoxic activation of protein kinase C (PKC) can upregulate autophagic flux thereby protecting cells from apoptotic cell death (Tan et al., 2012). Other stresses associated with obesity, such as inflammation and oxidative stress, can also upregulate autophagy through various mechanisms (Filomeni et al., 2015; Qian et al., 2017). Autophagy induction in this context can be viewed as part of a cellular defense mechanism that is coordinated to maintain cellular homeostasis under obesity-associated stresses.

Efficient autophagy should result in decreased accumulation of autophagy substrates, such as lipid droplets and a ubiquitin adaptor protein p62/SQSTM1. However, in virtually all of the studies, these autophagy substrates were found to prominently accumulate during conditions of obesity and lipotoxicity (Gonzalez-Rodriguez et al., 2014; Park et al., 2014b; Yang et al., 2010). These findings suggest that obesity, in actuality, interferes with the autophagy process. Although early studies interpreted obesity-induced accumulation of autophagosomes as activated autophagy, this interpretation is currently being challenged, as many of these studies did not appropriately measure autophagic flux (Klionsky et al., 2016; Mizushima et al., 2010). For instance, pancreatic beta cells were originally reported to upregulate autophagosome formation in response to lipotoxic insults during obesity (Ebato et al., 2008; Lupi et al., 2002; Martino et al., 2012). However, it was later revealed that lipotoxicity inhibits the autophagic flux in these cells, and defective degradation is instead the main cause of autophagosome accumulation during obesity (Las et al., 2011; Mir et al., 2015). Also, in liver and kidney cells, excessive autophagosome accumulation during obesity was again revealed to be primarily due to decreased degradation (Park and Lee, 2014; Park et al., 2014b; Takabatake et al., 2017).

Interestingly, the mechanism of how lipotoxic insults interfere with autophagic flux is dependent on tissue type. In liver cells, the defect was observed at the autophagosomal-lysosomal fusion step; autophagosomes cannot fuse with lysosomes, primarily due to elevated levels of cytosolic calcium during lipotoxicity (Park et al., 2014b). Lipotoxic inhibition of SERCA is likely to be involved in this type of autophagy dysregulation (Czaja, 2015; Park and Lee, 2014). In addition to the calcium-dependent mechanism of inhibition, lipotoxicity and obesity can upregulate expression of Rubicon, a protein that can inhibit the fusion between autophagosomes and lysosomes (Tanaka et al., 2016). In contrast, kidney cells do not display defects in autophagosomal-lysosomal fusion in response to lipotoxicity or obesity (Yamamoto et al., 2017). Rather, they showed defects in lysosomal acidification, which is essential for the activity of lysosomal enzymes, suggesting that lysosomal degradative function was impaired during obesity (Yamamoto et al., 2017). Interestingly, lysosomal acidification was not found to become defective in liver cells after lipotoxicity (Park et al., 2014b). In pancreatic beta cells, defects in autophagosomal-lysosomal fusion and lysosomal acidification were both observed after lipotoxic insults (Las et al., 2011; Mir et al., 2015). Recent genetic study showed that autophagosomal-lysosomal fusion is not controlled by lysosomal acidification, indicating that these two processes are independently regulated by separate mechanisms (Mauvezin and Neufeld, 2015; Mauvezin et al., 2015). Therefore, the mechanism of how lipotoxicity alters autophagic flux seems to be different between tissues.

Most of the studies mentioned above focused on the effects of obesity and lipotoxicity on the conventional autophagy process, which involves bulk isolation of cytoplasm and membrane fusion with lysosomes (also known as macroautophagy). In addition to macroautophagy, obesity has also been demonstrated to interfere with chaperone-mediated autophagy (also known as CMA) (Kaushik and Cuervo, 2012), which directly targets specific proteins into the lysosome (Rodriguez-Navarro et al., 2012). In this context, obesity-associated changes in the lysosomal membrane lipid profile can alter lipid microdomains, which results in degradation of LAMP2A, the CMA receptor (Rodriguez-Navarro and Cuervo, 2012).

IMPACT OF AUTOPHAGY ALTERATION ON OBESITY-ASSOCIATED PATHOLOGIES

Considering the intricate relationship between obesity and the autophagy process, it can be easily presumed that autophagy plays a critical role in regulating the pathological outcomes of obesity. Obesity-associated pathologies are accompanied by prominent accumulation of lipid droplets, protein aggregates and damaged mitochondria, all of which are major substrates of autophagy. Therefore, it can be expected that autophagy abrogation would accelerate obesity-associated pathologies in multiple tissue systems.

Indeed, genetic autophagy ablation in liver resulted in several pathologies that resemble those observed in obesity-associated non-alcoholic steatohepatitis (NASH), such as protein inclusion formation, fat accumulation and liver injury (Komatsu et al., 2005; 2007; Singh et al., 2009a). Systemic reduction of autophagic activity through Atg7 haploinsufficiency accelerated progression of diabetic pathologies during obesity (Lim et al., 2014). Conversely, systemic overex-

pression of Atg5, which upregulates autophagy, protected mice from age-associated obesity and insulin resistance (Pyo et al., 2013). Liver-specific overexpression of Atg7 or TFEB was also shown to improve obesity-associated ER stress and insulin resistance, confirming the protective role of autophagy in the organ (Settembre et al., 2013; Yang et al., 2010). Pharmacological activation of autophagy, through rapamycin or carbamazepine, also alleviated fat accumulation and liver injury during alcoholic and non-alcoholic fatty liver conditions (Ding et al., 2010; Lin et al., 2013). Calcium channel blockers, which can restore autophagic flux inhibited by lipotoxicity and obesity, almost completely normalized liver fat level and insulin sensitivity during high fat diet (HFD)-induced obesity (Park et al., 2014b). Genetic deletion of Rubicon, which can alternatively restore autophagosomal-lysosomal fusion during obesity, also substantially ameliorated obesity-associated liver fat accumulation (Tanaka et al., 2016). Collectively, these results indicate that autophagy has a protective role against obesity-associated pathologies in liver.

However, mice with liver- or skeletal muscle-specific deletions of Atg7 paradoxically improved multiple obesity-associated pathologies, such as adipogenesis, insulin resistance and hepatic fat accumulation (Kim et al., 2013). This observation was explained by an increased production of FGF21 in autophagy-defective tissues, which improves metabolism through a tissue non-autonomous manner (Kim et al., 2013). Similarly, mice with liver-specific deletion of FIP200, another gene essential for ATG1-dependent autophagosome formation (Hara et al., 2008), showed decreased levels of hepatic steatosis upon HFD (Ma et al., 2013). These results indicate that, even though physiological autophagy is important for suppressing obesity-associated metabolic derangements, complete ablation of autophagy can induce compensatory mechanisms that can protect against the detrimental consequences of obesity and autophagy dysfunction.

Autophagy may also play a role in modifying the pathological outcome of obesity in non-parenchymal cells of liver, such as macrophages (Liu et al., 2015) and hepatic stellate cells (Hernandez-Gea et al., 2012). Loss of autophagy in macrophages can promote inflammatory macrophage polarization, provoking inflammation at both systemic and hepatic levels (Liu et al., 2015). This exacerbated liver injury upon HFD and lipopolysaccharide (LPS) challenges (Liu et al., 2015). Autophagy in macrophages is demonstrated to be important for suppressing atherosclerosis, another obesity-associated pathology in the cardiovascular system (Liao et al., 2012; Razani et al., 2012). These results, as well as other results indicating that autophagy in immune cells is important for suppressing inflammation (Netea-Maier et al., 2016), suggest that autophagy in macrophages has a role in limiting obesity-associated inflammation and pathologies. In contrast, autophagy in hepatic stellate cells has a function in promoting fibrotic liver pathologies (Hernandez-Gea et al., 2012). Upon liver injury, hepatic stellate cells upregulate autophagy to utilize lipid droplets as an energy source, and this process is required for full activation of the hepatic stellate cells that results in promotion of liver fibrosis (Hernandez-Gea et al., 2012). Autophagy-mediated degradation of p62/SQSTM1 can also contribute to fibrosis aggravation because p62/SQSTM1 suppresses fibrogenic processes through vitamin D receptor activation (Duran et al., 2016). Consequently, inhibition of autophagy in hepatic stellate cells decreased liver fibrosis after chemical injuries (Hernandez-Gea et al., 2012).

The homeostatic role of autophagy was also established in mice with the pancreatic beta cell-specific deletion of Atg7. Autophagy inhibition resulted in beta cell dysfunction and reduced mass, leading to diabetic phenotypes such as hyperglycemia and glucose intolerance due to decreased insulin production (Ebato et al., 2008; Jung et al., 2008). These phenotypes were aggravated when combined with dietary or genetic obesity induction (Ebato et al., 2008; Quan et al., 2012). The aggravation of beta cell pathologies was partially due to the damages caused by excessive ER stress (Bartolome et al., 2012; Quan et al., 2012).

Finally, autophagy ablation in adipose tissue produced some beneficial effects against obesity phenotypes. Because autophagy is required for adipogenic processes, autophagy ablation decreased adipogenesis thereby reduced body weight gain during obesity (Singh et al., 2009b; Zhang et al., 2009). In addition, autophagy is potentially involved in whitening of adipose tissue by reducing the amount of mitochondria through autophagic elimination. Therefore, suppression of autophagy led to retention of mitochondria in white adipose tissue, resulting in increased energy expenditure and subsequent reduction in body weight (Singh et al., 2009b). Therefore, similar to the cases observed in skeletal muscle and liver, autophagy suppression in adipose tissue paradoxically produced beneficial effects during the conditions of obesity (Singh et al., 2009b; Zhang et al., 2009).

CONCLUSION

The large amount of recent literature, among which some were discussed above, focused on understanding the intricate relationship between obesity, autophagy dysfunction and their pathological consequences (Fig. 1). Although nutritional abundance can generally suppress autophagy initiation, stress insults associated with obesity can stimulate autophagy as a stress defense mechanism. In addition, lipotoxic insults can interfere with autophagy by inhibiting autophagosome degradation through multiple independent mechanisms. Although defective autophagy generally leads to deterioration of metabolic homeostasis, autophagy inhibition in certain pathophysiological context can paradoxically upregulate compensatory pathways that can be beneficial for defending against the consequences of obesity.

Obesity and metabolic syndrome are not a homogeneous disorder in both humans and animal models. The composition of diets and the level of sedentariness are critical variables for determining the role of autophagy in homeostasis of different tissues. For instance, saturated and unsaturated fatty acids can produce distinct pathogenetic effects, while they have similar caloric values and both are obesogenic. Levels of physical activity can be also important for determining the metabolic contribution of different tissues as their

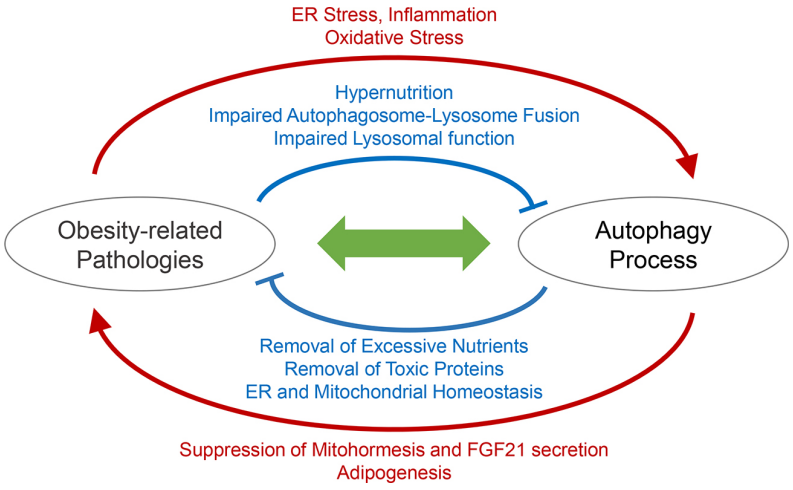

Fig. 1. Relationship between Obesity and Autophagy. Sophisticated interaction between autophagy and obesity-associated pathologies is schematically illustrated.

rates of energy expenditure can be altered. Understanding the contribution of each of these factors have in autophagic regulation and pathological outcomes will be important for designing tailored therapeutic strategies for obese patients. Individual obese patients will have autophagy alterations through different molecular mechanisms, which may necessitate the development of personalized medicine that can precisely restore the specifically defective processes.

ACKNOWLEDGMENTS

This work was supported by the NIH (R01DK102850 and R21OD018265) to J.H.L.

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