PERSPECTIVE

Autophagy and Obesity-Related Lung Disease

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Abstract

Obesity-related disease is a significant source of premature death and economic burden globally. It is also a common comorbidity in patients suffering from lung disease, affecting both severity and treatment success. However, this complex association between obesity and the lung is poorly understood. Autophagy is a self-recycling homeostatic process that has been linked to beneficial or deleterious effects, depending on the specific lung disease. Obesity affects autophagy in a tissue-specific manner, activating autophagy in adipocytes and impairing autophagy in hepatocytes, immune cells, and pancreatic β-cells, among others. Obesity is also characterized by chronic low-grade inflammation that can be modulated by the pro- and antiinflammatory effects of the autophagic machinery. Scant evidence exists regarding the impact of autophagy in obesity-related lung diseases, but there are communal pathways that could be related to disease pathogenesis. Important signaling molecules in obesity, including IL-17, leptin, adiponectin, NLRP3 inflammasome, and TLR-4, have been implicated in the pathogenesis of lung disease. These mediators are known to be modulated by autophagy activity. In this perspective, we highlight the recent advances in the understanding of autophagy in obesity-related conditions, as well as the potential mechanisms that can link autophagy and obesity in the pathogenesis of lung disease.

Keywords: autophagy; obesity; lung disease; inflammation; lipid metabolism

Clinical Relevance

Autophagy is a well-known important factor in lung disease pathogenesis, but its relationship with obesity in lung diseases has not been studied. With this perspective, we review what is known to date and propose future directions in this field.

Obesity is the result of an imbalance between energy intake and energy output and has reached pandemic level in developed countries. According to the World Health Organization, the prevalence of obesity has doubled since 1980, with 13% of the adult population being obese (1). Obesity accounts for 5.5–6.8% of the health budget in the United States, and obesity-related disease and organ dysfunction is a significant source of premature death and life years lost relative to life expectancy (2). In addition to well-known associated disorders such as type 2 diabetes mellitus, hepatic steatosis, and atherosclerosis, obesity has been implicated as a modulating factor in a variety of other human diseases. Obesity has been linked to increased incidence of colon, prostate, and hematologic malignancies (3), and worsening autoimmune conditions (4), but it may be protective in the critically ill and in vascular disorders such as postmyocardial infarction (5) or stroke (6).

Obesity-associated lung disease presents unique phenotypes among different lung pathologies, affecting both the severity of disease and its response to treatment. Obstructive sleep apnea (OSA) and obesity hypoventilation syndrome are the two diseases most intimately associated with obesity (7, 8). However, obesity has also been linked to several other lung pathologies, such as asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. Obese patients have a 50% higher incidence of asthma compared with nonobese patients (9). These patients tend to have a neutrophilic and Th17-driven inflammatory response that is less responsive to treatment with glucocorticoids (10–12). Patients with

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idiopathic pulmonary fibrosis (IPF) and obesity have higher waitlist mortality and 90-day post-transplant mortality (13, 14). Obese patients with acute respiratory distress syndrome have longer duration of mechanical ventilation and intensive care unit stays but have mortality rates similar to those of nonobese patients (15). In contrast, patients with COPD and obesity have lower in-hospital, in-hospital mortality, and readmission rates (16, 17).

This complex association between adipose tissue and the lung is poorly understood. Recently, autophagy, the highly conserved degradation of intracellular organelles and proteins, has been shown to play an important role in both obesity and pulmonary disease pathogenesis. This perspective review focuses on the functional role of autophagy-obesity–related pulmonary disease states.

Autophagy

Autophagy

Autophagy is a vital cellular process that degrades and recycles intracellular components through lysosomal degradation (18). Cytosolic material such as damaged organelles, lipid droplets (LDs), foreign pathogens, or unwanted cytosolic proteins are enveloped in double-membrane autophagosomes that fuse with lysosomes for degradation. This degradative process is coupled with conserving energy and key nutrients for cellular homeostasis and function, which confers a prosurvival effect. Autophagy can be regulated by numerous pathologic conditions such as infection, environmental stress, malignancy, as well as by metabolic derangement including starvation and obesity (19). There are unique autophagy pathways that involve receptors that confer selectivity to recognize ubiquitinated-tagged cargo through ubiquitin-binding domains and link them to double-membrane autophagosomes through light chain 3 (LC3) interacting regions (20).

Selective Autophagy

Selective autophagy denotes the removal or degradation of specific cellular organelles or components such as stressed endoplasmic reticulum (ER) (ER-phagy) (21–24), mitochondria (mitophagy) (25–28), LDs (lipophagy) (29–31), aggregated misfolded proteins (aggrephagy) (32–35), and microbes (xenophagy) (36–39). Furthermore, polyubiquitin chains are generated on the outer mitochondrial membrane during mitochondrial stress (40). Recruitment of additional proteins such as PINK1 and Parkin contribute to the generation of autophagosome-mediated degradation of mitochondria, leading to mitophagy (25). Impairment in mitophagy can lead to the accumulation of damaged mitochondria and to increased production of reactive oxygen species to propagate further cell damage (41). Lipid stores can also be used through autophagy to release free fatty acids (FFAs) for β-oxidation and energy production (42). Autophagy contributes to LD and triglyceride (TG) breakdown through either engulfing small LDs into autophagosomes or pinching a small portion of a bigger LD. In hepatocytes, autophagy blockade led to the accumulation of triglycerides and LDs that were colocalized with autophagic-associated proteins and compartments (29). Autophagy participates in the regulation of innate and adaptive immunity, playing a crucial role in the resistance to bacterial, viral, and parasitic infections (43). Autophagy can participate in regulating inflammatory signaling in immune cells. Autophagy-deficient macrophages have increased IL-1β production after endotoxin stimulation (44). Autophagy-associated antiinflammatory properties (43) have a broad range of influence, exerting regulation over inflammasome activation (44), IFN response (45), nuclear factor (NF)-κB signaling (46), lymphocyte development and function (47), and the production of IL-1α, IL-1β, and IL-18 (48–51).

Molecular Mechanism of Autophagy

Numerous environmental factors regulate the activation or inhibition of autophagy. The mammalian target of rapamycin (mTOR) negatively regulates autophagy when there is an abundance of nutrients or growth factors (52). During starvation, AMP-activated protein kinase inhibits mTOR and activates uncoordinated-51–like protein kinase initiation complex (53), which enhances the activity of the Beclin 1 interacting complex that consists of Beclin 1 (BCL2 family proteins), VPS34 (a class III phosphatidylinositol-3 kinase), and ATG14L, leading to nucleation and formation of the autophagosome by increasing PI3P levels. The elongation of the autophagosome membrane requires two ubiquitin-like conjugation systems. The first is the ATG5–ATG12 complex, which is conjugated by ATG7 and ATG10 enzymes. The second requires ubiquitin-like protein microtubule–associated protein 1 LC3, also called ATG8, which is cleaved by ATG4B into LC3B-I and then converted to LC3B-II when conjugated with phosphatidylethanolamine by ATG3 and ATG7 (19). Conversion of LC3-I to LC3-II is a classic hallmark of autophagosome formation. Once the autophagosome is complete, it fuses with lysosomes to form autophagolysosomes for content degradation (Figure 1) (53).

Autophagy and Obesity

In the past decade, many advances have been made in the understanding of autophagy in the pathogenesis of human disease (19, 53–56). Obesity creates a chronic low-grade inflammatory state (57) that potentially can be modulated by autophagy-associated pathways. Regulation of tissue-specific autophagy has been shown to be critical in the development of obesity and obesity-associated metabolic disorders (58). $Atg7^{+/-}$ heterozygous mice are more prone to metabolic syndrome and inflammasome activation (59). Monoallelic loss of Beclin 2, which participates in autophagy, results in obesity, impaired glucose tolerance, and decreased insulin sensitivity (60).

Adipose tissue is a key regulator of lipid storage and is a major endocrine organ of the body. Obesity and high-fat diet (HFD) feeding up-regulates autophagy in adipocytes through induction of mitochondrial and ER stress (61). Aberrant autophagy activation leads to defective browning of the adipose tissue, diminishing its thermogenic capacity (61) and metabolic profile (62, 63). Autophagy also plays an important role in adipogenesis and differentiation. Stimulation of autophagy favors white adipocyte differentiation, whereas autophagy blockade favors brown adipocyte differentiation (64, 65). Adipocyte-specific $Atg7^{-/-}$ mice had lower baseline white adipose tissue (WAT) and body weight and improved metabolic profiles and were more resistant to HFD-induced obesity (64, 65). In humans, autophagy is up-regulated in adipocytes of obese patients with type 2 diabetes mellitus or insulin resistance, as evidenced by increased autophagy markers, associated transcription factors, and increased colocalization of LDs with LC3 in autophagosomes (66–70). Interestingly

though, autophagy markers have also been found to be low in obese patients before bariatric surgery (71). Pharmacologic blockade of autophagy by mineralcorticoid receptor antagonists prevents weight gain after HFD and increases brown adipocyte transcripts and adipocyte count. Treatment with lipoxins in obese mice down-regulates autophagy in WAT, attenuates hepatic steatosis, and reduces inflammation (72, 73). Thus, autophagic activity in adipocytes promotes obesity through white adipocyte differentiation and augments obesity-associated disorders such as insulin resistance, hepatic steatosis, and inflammation.

Hepatocytes convert FFAs into TGs for storage in LDs (74). Blockade of lipophagy leads to accumulation of TGs and LDs within autophagic compartments (29). Lipotoxicity, caused by either exogenous accumulation via HFD or endogenous accumulation via TG/LD, contributes to further inhibition of autophagy and worsens TG/LD accumulation (Figure 2) (29, 75). In obesity models, autophagy markers are down-regulated in hepatocytes compared with control subjects. Blockade of autophagy in hepatocytes leads to worsening of metabolic diseases such as insulin resistance, hepatic steatosis, and ER stress (76). Thus, autophagic activity in hepatocytes has a beneficial role and protects against obesity-associated metabolic disorders such as hepatic steatosis, insulin resistance, and impaired glucose metabolism.

FFAs can promote the generation of harmful reactive oxygen species in β-cells

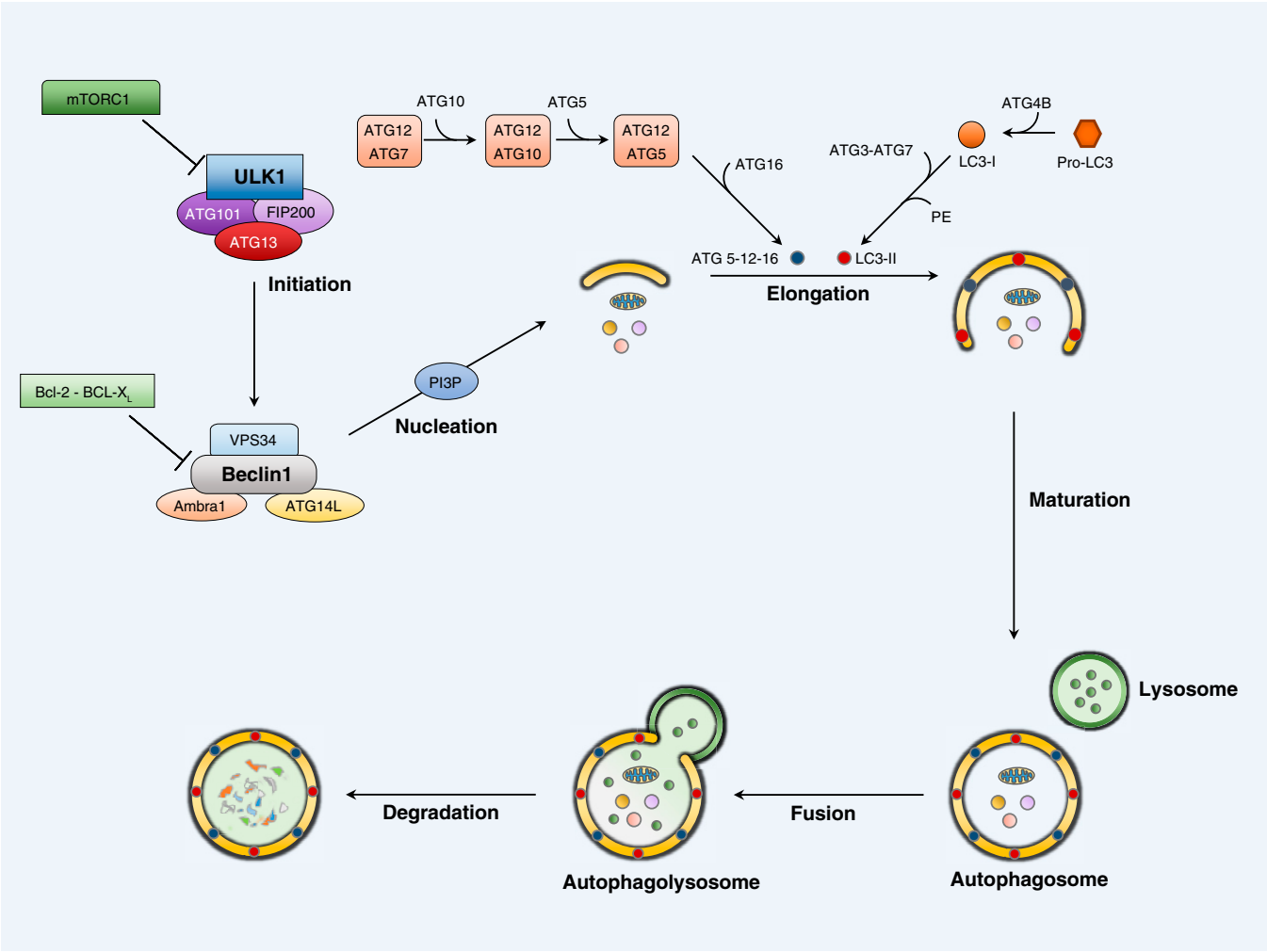

Figure 1. Molecular mechanism of autophagy. Environmental signals modulate mammalian target of rapamycin (mTOR) complex 1 (mTORC1), negatively regulating autophagy by inhibiting the uncoordinated-51–like kinase 1 (ULK1) complex consisting of ULK1, ATG101, ATG13, and FIP200. Starvation and low ATP levels down-regulate mTOR and directly stimulate the ULK1 complex. The ULK1 complex positively regulates autophagy by activating the Beclin 1 interacting complex, which consists of Beclin 1 (BCL2 family proteins), VPS34 (a class III phosphatidylinositol-3 kinase), and ATG14L. This increases the levels of phosphatidylinositol 3-phosphate (PI3P), which promotes the nucleation of autophagosomal membrane. The elongation of the autophagosome membrane requires two ubiquitin-like conjugation systems. The first is the ATG5–ATG12 complex, which is conjugated by ATG7 and ATG10 enzymes. The second one requires the ubiquitin-like protein microtubule–associated protein 1 light chain 3 (LC3), also called ATG8, which is cleaved by ATG4B into LC3B-I. LC3B-I turns into the active LC3B-II after conjugation with phosphatidylethanolamine by ATG3 and ATG7. Once the double-membrane autophagosome is complete, it fuses with a lysosome to form the autophagolysosome to degrade the autophagosome contents. ATG, autophagy-related protein; FIP200, focal adhesion kinase family interacting protein of 200 kD; VPS34, vacuolar protein sorting 34.

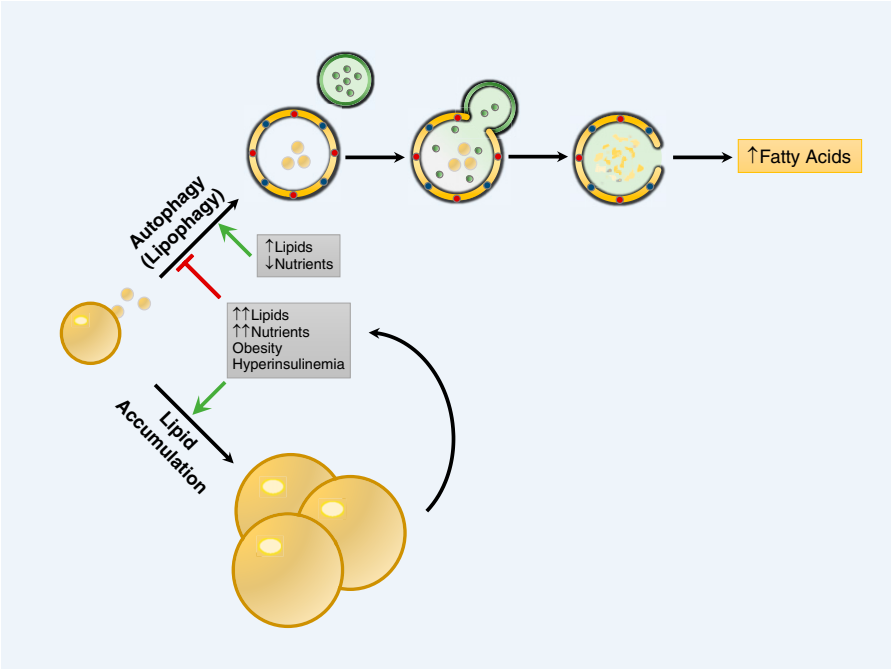

Figure 2. Role of autophagy in lipid metabolism in the liver. In hepatocytes, autophagy plays an important role in lipid turnover from lipid droplets. In starvation, autophagy degrades lipid droplets to increase free fatty acids and fuel β-oxidation. In obesity-related conditions such as hyperinsulinemia and lipid accumulation, autophagy is inhibited, which causes a predisposition toward more lipid accumulation and, in turn, further autophagy inhibition that, in organs such as the liver, can lead to hepatic steatosis.

(77). Autophagy is up-regulated as a defense mechanism, protecting β-cells on FFA exposure (78). However, excessive FFAs can subsequently inhibit autophagy through impaired autophagosome maturation and turnover (79). Autophagy in skeletal muscle potentiates exercise-induced improvements in glucose homeostasis and insulin sensitivity in HFD mice (80). Controversy remains as to whether autophagy may be protective in non–exercise-related HFD models (81, 82). HFD impairs autophagy in the medial-basal hypothalamus, the central control for metabolic physiology and feeding behavior. Selective autophagy blockade of the hypothalamus leads to obesity and insulin resistance in mice. Starvation induces autophagy in agouti-related protein (AgRP) neurons, which produce AgRP to increase food intake (83). Autophagy blockade in these neurons during starvation attenuates AgRP release and confers a lean phenotype (84). Conversely, in pro-opiomelanocortin neurons that suppress food intake (83), autophagy blockade through ATG7 or ATG12 leads to increased obesity from impaired lipolysis and disrupted glucose homeostasis (85, 86).

In summary, autophagy plays an important role in regulating obesity-related metabolic dysfunction. Lipid overload can affect autophagy, which can lead to decreased lipophagy, decreased mitochondrial turnover and increased ER stress, low-grade inflammation, and finally, insulin resistance, although differences in autophagy regulation can be cell specific (Figure 3). Currently, no studies have examined the effect of HFD on autophagy in the lung.

Autophagy and Pulmonary Disease

Asthma. Significant advancements have been made in the understanding of autophagy in the pathogenesis of pulmonary disease, often through modulation of the inflammatory response. Autophagy has been studied in asthma, COPD, IPF, acute lung injury, OSA, and several other pulmonary diseases (87). Dendritic cell–specific ATG5–deficient mice exposed to house dust mites develop severe IL-17A–dependent, steroid-resistant asthma and unprovoked airway hyperresponsiveness (AHR) (88). However, during virally mediated asthma exacerbations, exuberant autophagy may decrease IFN-γ and increase viral load (89). In human subjects, single nucleotide polymorphisms in the ATG5 gene have been associated with asthma (90). Markers of autophagy were also elevated in the sputum granulocytes and eosinophils of subjects with asthma (91).

COPD. Markers of autophagy are elevated in patients with COPD from cigarette smoke or α-1 antitrypsin deficiency (92). Autophagy was also up-regulated *in vitro* (92–98) and *in vivo* in models of COPD and chronic bronchitis (95, 99). Inhibition of autophagy (93, 94, 100) and mitophagy (101) attenuate cigarette smoke–induced lung injury and chronic bronchitis. However, aggregophagy and xenophagy seem to be protective for disease pathogenesis (102, 103).

Pulmonary Fibrosis. Autophagy is associated with the degradation of collagen and is protective in *in vivo* models of pulmonary fibrosis (104–107). TGF-β, one of the hallmark cytokines of fibrosis, can inhibit autophagy through mTOR (108), favoring collagen deposition in fibroblasts (109). Autophagy marker levels are low in the lungs of patients with IPF (109, 110). Mitophagy can also have a potentially beneficial effect in the pathogenesis of pulmonary fibrosis. PINK1-deficient mice were susceptible to lung fibrosis induced by bleomycin (111, 112). The role PINK1 expression plays in the lungs of patients with IPF is controversial because there are reports on high (111) and low (112) levels related to ER stress (112).

Inhibition of autophagy and mitophagy decreases cell viability in acute lung injury (113, 114). Up-regulation of autophagy by low-dose cytoprotective carbon monoxide exposure can inhibit cell death in lung epithelial cells (115). In chronic/recurrent hypoxia animal models of OSA, autophagy is induced and may be protective for cardiac function (116). However, the activation of mitophagy can be detrimental in hypoxemic conditions (117).

Impact of Autophagy in the Pathogenesis of Obesity-related Lung Disease

Obesity and many pulmonary diseases share common signaling pathways related to

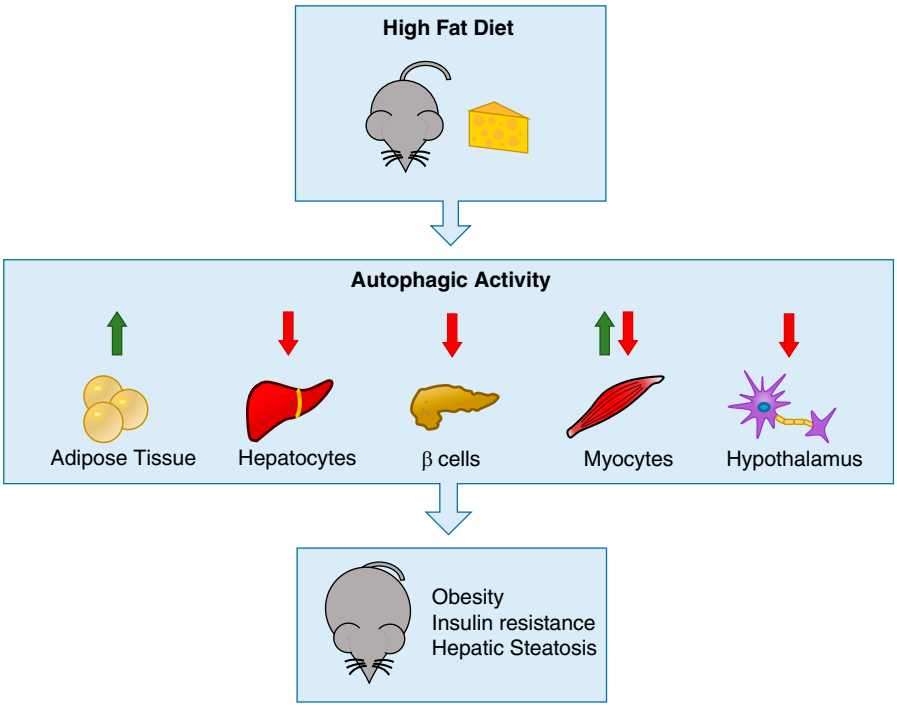

Figure 3. Tissue-specific regulation of autophagy under high-fat diet conditions. Under high-fat diet conditions, mice have tissue-specific changes in autophagy. In adipose tissue, there is an increase in autophagic activity as a response to endoplasmic reticulum stress, leading to degradation of the antiinflammatory adipokine adiponectin. In hepatocytes, β cells, and hypothalamic neurons, there is decreased autophagy under a high-fat diet, leading to lipid accumulation, β-cell toxicity, and inflammation. In myocytes under exercise, there is an increase in autophagy, leading to decreased insulin resistance. Thus, aberrant autophagy contributes to obesity disease pathogenesis, leading to insulin resistance, hepatic steatosis, and inflammation.

inflammation. Several signaling molecules in obesity, including IL-17, leptin, adiponectin, NLRP3 inflammasome, and TLR-4, have been implicated in the pathogenesis of lung disease. Autophagy regulates inflammation through a variety of mechanisms (47). In obesity, autophagy impairment in the bone marrow derived macrophages and Kupfer cells of mice fed an HFD produces increased release of proinflammatory cytokines and macrophage proinflammatory polarization (118). Autophagy-deficient mice have increased inflammasome activation (59). In addition, autophagy deficiency in the hypothalamus induces IKKβ/NF-κB activation and inflammatory changes in the hypothalamus after HFD (119). Autophagy blockade in cultured human adipocytes leads to increased IL-1β, IL-6, and IL-8 secretion (69) and to the activation of ER stress–induced autophagy (120).

IL-17 is a known mediator of neutrophilic inflammation in the airways in various lung diseases (121, 122). IL-17 is also up-regulated in obesity associated with altered dendritic cell function (123). IL-1β is required for the production of IL-17A by $CD4^+$ T cells. Autophagy decreases IL-1β (44, 124) by sequestering pro–IL-1 β, thus down-regulating IL-17A production (48). In obesity-associated asthma, IL-17A plays an essential role in disease severity and is required for AHR in a murine model because IL-17–deficient mice do not develop asthma under HFD (125). Increased IL-17 levels are correlated to worsening the exacerbating fibrosis in bleomycin-induced lung injury (126, 127). Loss of autophagy in dendritic cells leads to IL-17A–driven AHR in a murine asthma model (88). After infection with respiratory syncytial virus, $lc3b^{-/-}$ dendritic cells have altered innate cytokine production, leading to a Th17-skewed $CD4^+$ T-cell response and lung injury (128). Similarly, airway epithelial cells deficient in LC3B had enhanced inflammasome activation and increased IL-1 and IL-17A production after respiratory syncytial virus infection (128). IL-17 is increased in the bronchial mucosa of patients with COPD (122, 129, 130) and asthma (130). Genetic deletion of IL-17 in mice was protective against cigarette smoke–induced lung inflammation and apoptosis of type II alveolar epithelial cells (131).

Innate lymphoid cells group 3 cells are lymphoid cells that lack B or T receptors and produce IL-17A as their signature cytokine (132). In mice under HFD conditions, innate lymphoid cells group 3 has been shown to be present in the lungs and can be stimulated by IL-1β produced by lung or adipose tissue macrophages to produce AHR (125). IL-17A has also been shown to play an important role in pulmonary fibrosis pathogenesis by stimulating collagen production. Autophagy is activated by IL-17 inhibition, promoting degradation of collagen in lung epithelial cells (133). IL-17 can also inhibit autophagy in lung epithelial cells by regulating phosphorylation of BCL2 (134). HFD conditions can cause interstitial disease similar to sarcoidosis and the progressive development of lung fibrosis (135). Thus, the regulation of IL-17 by autophagy could be altered in obesity and could lead to the pathogenesis of pulmonary diseases such as asthma and IPF (Figure 4A).

The secretion of IL-1β and IL-18 is regulated by the NLRP3 inflammasome (136). In obesity, the NLRP3 inflammasome is activated by obesity-associated "danger signals" and participates in the regulation of T cells in the adipose tissue, contributing to a proinflammatory state (137). NLRP3 has been shown to be up-regulated in the adipocytes of obese patients with metabolic syndrome (138). Autophagy can regulate inflammatory responses related to NLRP3 inflammasome (50) and target ubiquitinated inflammasomes for degradation (139), limiting inflammation. Under HFD conditions, FFAs are able to induce inflammasome-dependent IL-1β and IL-18 production and inhibit the autophagosome formation that results in impaired insulin signaling (140). In a hyperoxia model, NLRP3-deficient mice are resistant to oxidative damage, and interestingly, this resistance is correlated to PINK1 expression (114). NLRP3 inflammasome (as well as IL-17) is required to develop AHR in obese mice (125), but the relation between autophagy and NLRP3 under obesity conditions in other lung diseases has not been studied. Thus,

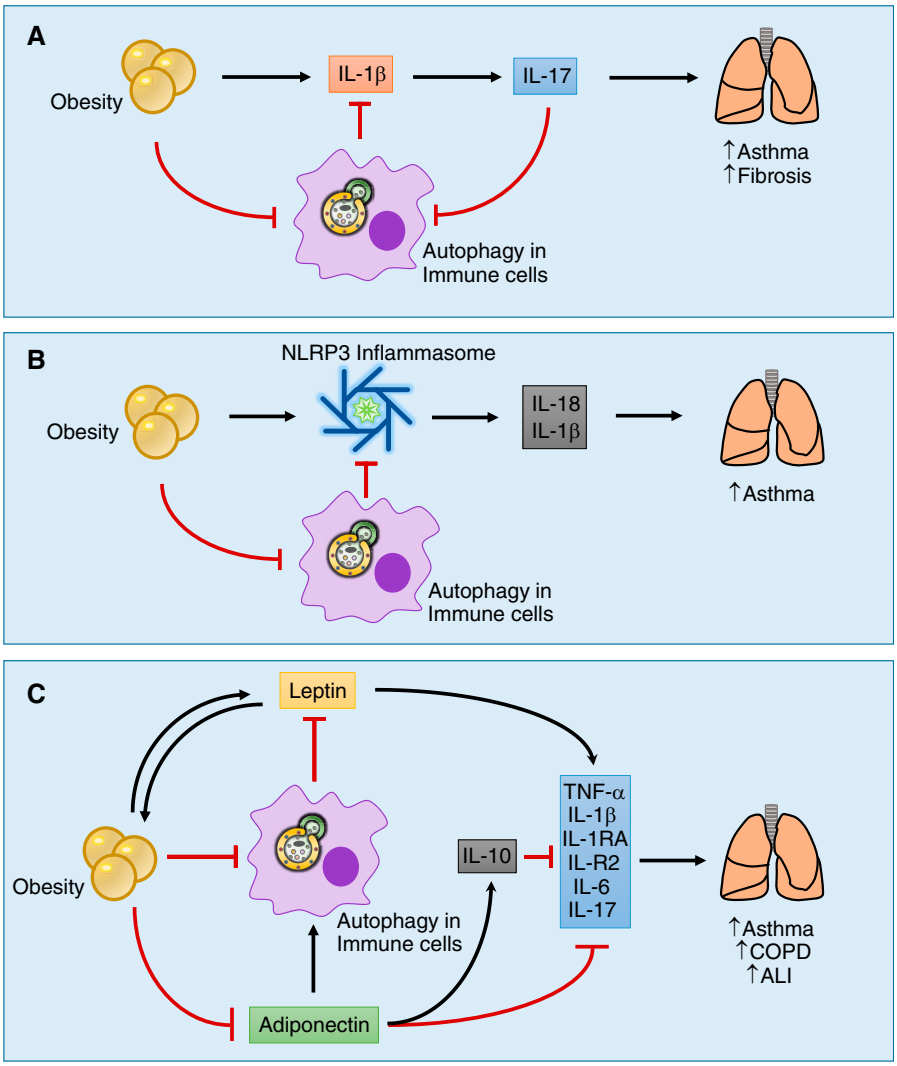

Figure 4. Proposed mechanisms of obesity- and autophagy-related pathogenesis of lung disease. (*A*) Obesity induces the production of inflammatory cytokines such as IL-1β by macrophages in the adipose or lung tissue, leading to the production of IL-17. IL-17 has been correlated with worsening lung inflammation and injury in diseases such as asthma and fibrosis. Autophagy can sequester pro–IL-1β, decreasing IL-1β production and thus negatively regulating IL-17 levels. (*B*) Obesity is characterized by NLRP3 inflammasome activation that increases the production of inflammatory cytokines such as IL-1β and IL-18, which has been shown to contribute to lung disease pathogenesis. Autophagy can inhibit inflammasome activation, thereby decreasing IL-1β and IL-18 production. (*C*) Adipocytes are characterized by adipokine production such as leptin and adiponectin. Under obesity conditions, leptin levels are increased as a result of leptin resistance. Leptin has systemic effects and can increase the production of inflammatory cytokines. Adiponectin is decreased in obesity. Adiponectin has antiinflammatory properties through increasing production of IL-10 and inhibits the production of proinflammatory cytokines such as TNF-α, IL-1β, IL-1RA, IL-R2, IL-6, and IL-17. ALI, acute lung injury; COPD, chronic obstructive pulmonary disease; NLRP3, nod-like receptor protein-3.

autophagy may act as a defense mechanism to limit obesity-associated inflammation and lung disease through the inhibition of the NLRP3 inflammasome–mediated IL-1β and IL-18 production (Figure 4B).

Obesity is correlated with higher levels of leptin, an adipokine that influences appetite. Leptin has also been shown to stimulate the production of inflammatory cytokines such as TNF-α, IL-1β, IL-1RA, IL-R2, and IL-6 in innate and adaptive immunity (141, 142). Airway epithelial cells express receptors for leptin and adiponectin, suggesting a potential ability to respond to this systemic mediator (143). Leptin levels have been correlated with the severity of COPD (143), asthma (143), and acute lung injury (ALI) (144). In patients with COPD, increases in leptin levels correlate with a proinflammatory state (145). Leptin polymorphisms have also been associated with COPD severity (146). Leptin has been shown to promote a Th17-mediated inflammatory response in lupus-prone mice (147) and to inhibit autophagy in $CD4^+$ T cells (148). Inhibition of autophagy can increase leptin levels (85, 86), suggesting that leptin and autophagy regulate one another, contributing to both obesity and pulmonary disease (Figure 4C).

Adiponectin is another key adipokine in metabolism that is classically down-regulated in obesity. HFD/obesity-associated ER stress promotes the degradation of adiponectin through autophagy, and this has been associated with glucose intolerance or diabetes in human studies (149, 150). Adiponectin has also been shown to have antiinflammatory effects such as suppression of TNF-α, IL-6, and NF-κB and up-regulation of IL-10 (141). Mice deficient in adiponectin have increased IL-17A–mediated neutrophilic infiltration of the lung (151). Adiponectin has also been shown to regulate IL-17A release in other diseases such as psoriasis (152). Adiponectin is a known positive regulator of autophagy in myocytes (81), and adiponectin-induced autophagy has been found to have beneficial antiinflammatory effects in cardiovascular diseases (153, 154), but currently, no studies have examined its effects on autophagy in the lung. In macrophages stimulated with LPS, adiponectin can inhibit autophagy-mediated TNF-α production (155). Treatment with adiponectin can abolish AHR in asthma murine models (156) and decrease inflammation in ALI murine models (157, 158). Thus, adiponectin may play a role in augmenting autophagy-mediated immune modulating and attenuating obesity-associated inflammatory cytokine release and lung injury (Figure 4C).

TLR-4 signaling and ER stress are related to the proinflammatory response in obesity. HFD can stimulate TLR-4, which, in turn, increases the expression of proinflammatory cytokines that lead to mitochondrial and ER stress (61). ER stress is one of the most important stimulators of autophagy in WAT under obesity conditions (149, 150). However, TLR-4 has been shown to be protective

for the maintenance of normal lung architecture because TLR-4–deficient mice have emphysema and increased autophagy levels after cigarette smoke exposure (95). In a murine model of hypercholesterolemia, mice were found to develop emphysema and TLR-4 signaling activation after feeding with HFD (159). Impairment of TLR-4–dependent autophagy activation in the bleomycin pulmonary fibrosis models exacerbates pulmonary fibrosis through the inhibition of autophagy-associated collagen degradation. This effect can then be reversed when autophagy is stimulated by rapamycin (160). All the above suggest that TLR-4 can exert different regulatory functions over autophagy, depending on the stimuli such as CS, FFAs, or profibrotic mediators.

Future studies should focus on the regulation of these obesity-related inflammatory mediators by stimulation and inhibition of autophagy under HFD conditions in animal models of asthma, IPF, ALI, OSA, and COPD. We hypothesize that the stimulation of autophagy in these models may attenuate HFD or obesity-associated lung injury.

Conclusions

Autophagy and obesity-related inflammation are involved in pulmonary disease pathogenesis. The growing interest in autophagy and its role in obesity-associated pulmonary disease is evolving. Obesity promotes a systemic proinflammatory environment that is exacerbated by obesity-associated suppression of autophagy. Defective autophagy leads to dysregulated IL-17, leptin, adiponectin, TLRs, and NLRP3 inflammasome activation, as well as to defective mitochondrial accumulation and persistent ER stress, potentially leading to worse lung injury. Currently the role of autophagy in obesity-related lung disease is still unclear, and efforts to identify these links, given the high prevalence of obesity among the world population, are needed. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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