Autophagy: Friend or Foe in Lung Disease?

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Abstract

Autophagy is a highly conserved process by which cells can recycle organelles and proteins by degrading them in the lysosomes. Although autophagy is considered a dynamic system responsible for cellular renovation and homeostasis under physiological conditions, it is increasingly clear that autophagy is directly relevant to clinical disease. During disease progression, autophagy not only serves as a cellular protective mechanism but also can represent a harmful event under certain conditions. In addition, although autophagy can act as a nonselective bulk degradation process, recent research shows that autophagy can selectively degrade specific proteins, organelles, and invading bacteria, in processes termed "selective autophagy." Selective autophagy has drawn the attention of researchers because of its potential importance in clinical diseases. In this article, we outline the most recent studies implicating autophagy and selective autophagy in human lung diseases, including chronic obstructive pulmonary disease, pulmonary hypertension, idiopathic pulmonary fibrosis, and sepsis. We also discuss the relationship between autophagy and other molecular mechanisms related to disease progression, including programmed necrosis (necroptosis) and the inflammasome, an inflammatory signaling platform that regulates the secretion of IL-1β and IL-18. Finally, we examine the dual nature of autophagy and selective autophagy in the lung, which have both protective and injurious effects for human lung disease.

Keywords: autophagy; ciliophagy; inflammasome; mitophagy; necroptosis

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Autophagy is a lysosomal degradation system that engulfs cytoplasm and organelles by complex reorganization of subcellular membranes to form a new organelle: the autophagosome (Figure 1). Autophagosomes fuse with lysosomes and thereby deliver their contents for degradation (1). Although autophagy can function as a recycling system for metabolic precursors to promote cell survival, this process has also been implicated in clinical diseases (2). Autophagy is known to exert both protective and injurious effects in a variety of different models of disease, suggesting that its role in human diseases is complex (Table 1).

Once autophagy was simply considered as a nonspecific homeostatic cellular process; however, increasing evidence suggests that autophagy can represent a more selective process than originally anticipated. Recently, we and others have revealed the importance of selective autophagy pathways in chronic obstructive pulmonary disease (COPD); including mitophagy and ciliophagy (Figure 2) (3–5). Mitophagy refers to the specific autophagic elimination of mitochondria in which damaged or depolarized mitochondria are targeted for degradation (6). Parkin and phosphatase and tensin homolog (PTEN)-induced putative kinase protein 1 (PINK1) have been identified as two major mitophagy-related regulatory proteins. Ciliophagy is an autophagy-dependent pathway that regulates cilia length (4). Impaired airway clearance caused by ciliophagy-regulated cilia shortening may prevent the elimination of pathogens from the airways, resulting in recurrent respiratory infections that exacerbate COPD. Other forms of selective autophagy that may be relevant to human diseases include the removal of pathogens (xenophagy) and the processing of protein aggregates (aggrephagy). Selective autophagy is an emerging field that, as discussed in this article, is expected to provide new insight into the pathogenesis of human lung disease.

Recent studies have revealed that autophagy or selective autophagy can regulate other cellular pathways. In lung diseases, autophagy-regulated apoptosis may contribute

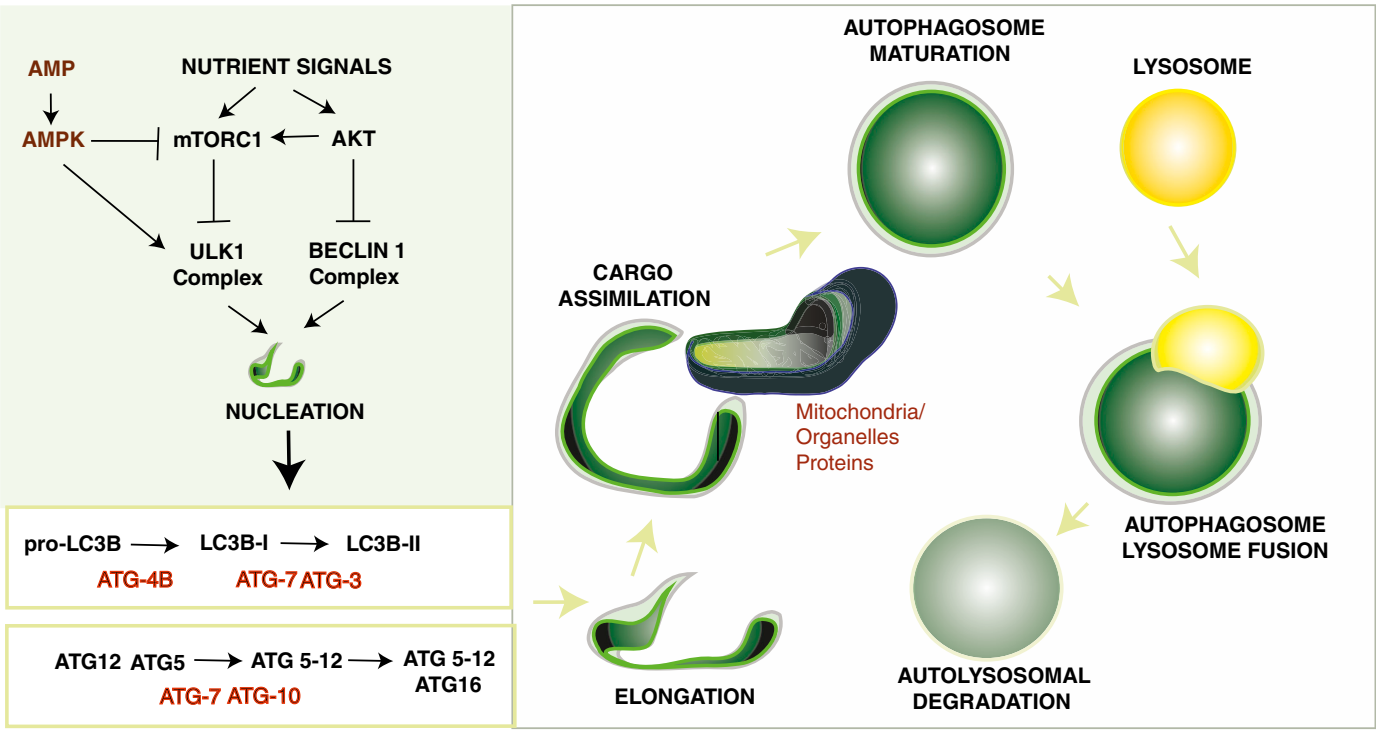

Figure 1. Autophagy pathway. Autophagy is a regulated process that responds to regulation by nutrient signals. Autophagy responds to negative regulation by growth factor stimuli that activate the phosphatidylinositol-3-kinase (PI3K/AKT) pathway, which up-regulates the mTOR pathway and down-regulates the Beclin1 complex. Autophagy responds to up-regulation by depletion of cellular energy charge through the activation of the adenosine monophosphate (AMP)-activated protein kinase (AMPK). In response to elevated AMP levels, AMPK can inhibit mTORC1 and directly phosphorylate ULK1, leading to activation of autophagy. The antibiotic rapamycin induces autophagy by inactivating mTORC1. The initiation of autophagosome formation is also regulated by the autophagy protein Beclin 1 (Atg6). Beclin 1 associates with a macromolecular complex that includes hVps34, a class III phosphatidylinositol-3 kinase. Autophagosome elongation requires two ubiquitin-like conjugation systems, the ATG5-12 conjugation system, and the ATG8 (LC3) conjugation system, which are regulated by various ATG proteins. Autophagy protein LC3-II remains associated with the maturing autophagosome. The basic sequence of steps of autophagy include: (*1*) initiation and autophagosomal nucleation (formation of the phagophore); (*2*) elongation of the nascent autophagosomal membrane, to capture a cargo such as mitochondria; (*3*) maturation of the double-membraned autophagosomal structure with cargo assimilation; and (*4*) autophagosome-lysosome fusion, which is concluded by degradation of the autolysosomal contents.

to the pathogenesis of COPD (7). Although apoptosis was previously recognized as the sole form of programmed cell death, necrosis was considered as an uncontrolled cell death induced by extreme physical or chemical stress. However, emerging studies have demonstrated the existence of a genetically programmed and regulated form of necrosis, termed necroptosis (8). Interestingly, necroptosis is regulated by mitophagy, which may contribute to the pathogenesis of COPD (3). Moreover, autophagy has been implicated in the regulation of the inflammasome pathway (9). Inflammasomes represent an inflammatory signaling platform that regulates the maturation and secretion of proinflammatory cytokines (e.g., IL-1β and IL-18), which are implicated in sepsis (9, 10). The role of autophagy and selective autophagy processes, whether protective or deleterious, depend on the disease, and sometimes differ between cell types. In this review, we examine the considerable emerging evidence for the contribution of autophagy and selective autophagy in the pathogenesis of complex lung diseases. A better understanding of autophagy and selective autophagy as "double-edged swords" in disease pathogenesis will help design personalized therapies for the treatment of lung diseases.

Autophagy: Regulation and Function in Experimental and Human Lung Diseases

Chronic Obstructive Pulmonary Disease

The World Health Organization reported that more than 3 million people died of COPD in 2012, which is equal to 6% of all deaths globally that year; however, the pathogenesis of this disease remains incompletely understood. We previously analyzed comprehensive gene expression profiles in Global Initiative for Chronic Obstructive Lung Disease stage 2 versus stage 0 smokers, which revealed that autophagy-related protein, ATG8/microtubule-associated protein-1 light chain-3 (LC3), was a candidate gene that may serve as a potential molecular target in COPD (11). Our further investigation demonstrated a pivotal role for autophagy proteins in cigarette smoke (CS)-induced emphysema (7, 12). We demonstrated that autophagic vacuoles (autophagosomes/autolysosomes) were dramatically increased in COPD lung tissues using electron microscopy, a gold-standard method for the determination of autophagy, whereas little vacuole formation was evident in control tissues (12). The expression of the

Table 1. Role of autophagy in human lung diseases

Disease	Strain/Manipulation	Phenotype/Observation	References
COPD	C57Bl/6; chronic CS	Increased airspace enlargement associated with increased autophagy markers	7, 12
	LC3B$^{-/-}$ mice, chronic CS	Decreased epithelial cell apoptosis and airspace enlargement	7
	Becn1$^{+/-}$ mice, acute CS	Decreased cilia loss and airways dysfunction	4
	PINK1$^{-/-}$ mice, chronic and acute CS	Decreased epithelial cell necroptosis and airspace enlargement; decreased airways dysfunction	3
	Human COPD lung	Increased autophagosome formation and autophagy markers	12
	Human smokers (alveolar macrophages)	Impaired autophagy	14
	Human COPD bronchial epithelial cells	Increased basal autophagy, decreased autophagy in response to CS stimulation, accelerated cell senescence	18
PAH	C57Bl/6; hypoxia	Increased autophagy associated with indices of vascular dysfunction	23
	LC3B$^{-/-}$ mice, hypoxia	Worsened indices of pulmonary hypertension	23
	Human PAH	Increased autophagy markers	23
ILD	C57Bl/6; bleomycin, rapamycin	Reduced lung fibrosis relative to bleomycin alone	25
	PINK1$^{-/-}$ mice	Increased lung fibrosis in aging mice	31
	PINK1$^{-/-}$ mice, bleomycin	Increased susceptibility to bleomycin-induced pulmonary fibrosis relative to wild-type mice	32
	Human ILD	Reduced autophagy markers	25
Sepsis	C57Bl/6; CLP	Increased autophagy markers	47
	LC3B$^{-/-}$, LPS	Increased mortality, increased inflammasome cytokine production	9
	Beclin 1$^{+/-}$, CLP sepsis	Increased mortality	47

Definition of abbreviations: CLP = cecal ligation and puncture; COPD = chronic obstructive pulmonary disease; CS = cigarette smoke; ILD = interstitial lung disease; LPS = lipopolysaccharide; PAH = pulmonary arterial hypertension.

active form of LC3B, LC3B-II, as well as that of additional autophagy-related proteins Atg4, Atg5-Atg12, and Atg7 increased in human lung specimens from patients with COPD. Genetic depletion of the essential autophagy mediators, LC3B and Beclin 1, reduced cigarette smoke extract (CSE)-induced epithelial cell death. Moreover, LC3B-deficient mice exhibited significant basal airspace enlargement relative to wild-type littermate mice (7). To determine whether increased autophagosome formation correlated with autophagic activity in the lungs of CS-treated mice, we applied *in vivo* autophagic flux assays developed in our laboratory (13). Analysis of LC3B steady-state levels in a lysosome-enriched fraction of lung homogenates revealed the time-dependent increase in leupeptin-sensitive LC3B degradation *in vivo*, which persisted 24 hours after CS exposure, supporting the conclusion that CS caused a cumulative increase in autophagic flux in lung tissue (4). These data suggest that the CS-induced autophagy pathway may promote epithelial cell death, associated with emphysematous airspace enlargement, in chronic CS-exposed mice and in patients with COPD.

On the other hand, a previous study reported defective autophagy in CS-exposed macrophages (14). Such a deficit in autophagy was found in the alveolar macrophages of smokers, suggesting that impaired delivery of bacteria to lysosomes may lead to recurrent infections in patients with COPD. Interestingly, it has also been suggested that autophagy regulates cellular senescence. Although there is evidence that autophagy induction may accelerate the development of senescence, other studies suggest the opposite, that autophagy inhibition is permissive for senescence (15). As CS-induced cell senescence has been implicated in the pathogenesis of COPD (16, 17), a previous study has evaluated autophagy-regulated senescence in bronchial epithelial cells (18). Although 3-MA, an inhibitor of autophagy, enhanced CSE-induced senescence in primary human bronchial epithelial cells (HBEC), Torin-1, an inducer of autophagy, suppressed CSE-induced HBEC senescence (18). Furthermore, although baseline autophagy activity in HBEC from patients with COPD was significantly increased compared with those of HBEC from nonsmokers and smokers without COPD, autophagy induction in response to CSE exposure was significantly attenuated in HBEC from patients with COPD compared with that observed in HBEC from nonsmokers and smokers without COPD (18). These findings implicate that autophagy is insufficient in the lungs of patients with COPD, which accelerates epithelial cell senescence. Additionally, mTOR signaling has been linked to CS induced COPD/emphysema (19). mTOR is an evolutionarily conserved serine-threonine kinase that acts as a sensor of environmental and cellular nutrition and energy status, which also plays a crucial role in regulating autophagy (20). Rtp801, a stress-related protein triggered by adverse environmental conditions, was overexpressed in human emphysematous lungs and in lungs of mice exposed to CS (19). Rtp801 stabilized the assembly of the mTOR inhibitory complex TSC1-TSC2, resulting in the exacerbation of oxidative stress–induced cell death (19). In this study, the mTOR inhibitor rapamycin was protective in wild-type mice exposed to smoke, reducing alveolar inflammation. In contrast, rapamycin increased the number of apoptotic and inflammatory cells in room air–exposed wild-type mice and abrogated the protective effects of Rtp801 knockout in mice exposed to CS. These studies highlight that the timing and lung cell targets of mTOR inhibition may therefore be essential to define its beneficial and pathological roles in disease.

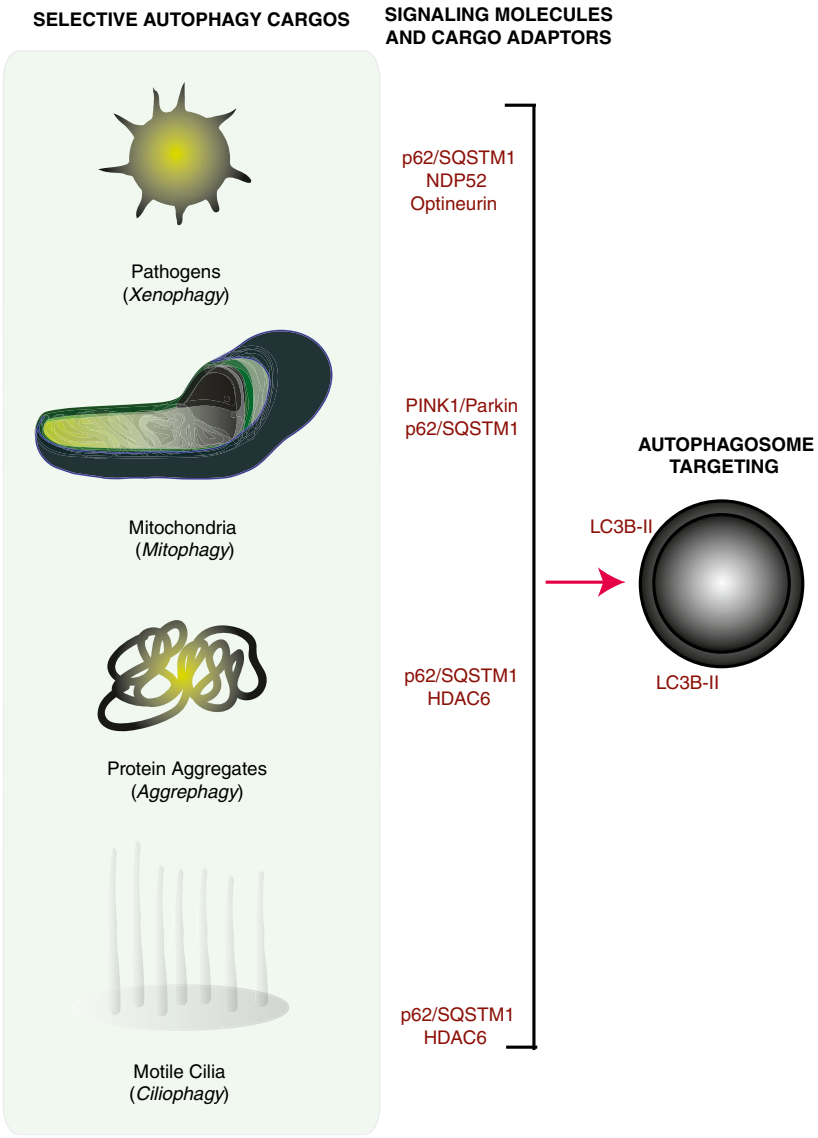

Figure 2. Selective autophagy pathways. Selective autophagy pathways have been described that are specific for the targeting and autophagosomal delivery of specific cargo. Selective autophagy cargoes and pathways may include pathogens (e.g., bacteria, viruses) (xenophagy), mitochondria (mitophagy), protein aggregates (aggrephagy), and motile cilia (ciliophagy). Phosphatase and tensin homolog (PTEN)-induced putative kinase protein 1 (Pink1) and Parkin are known activators of mitophagy. Selective autophagy cargo adaptors (e.g., p62/SQSTM1) have been identified that facilitate these pathways. Nuclear domain 10 protein 52 (NDP52) and optineurin have been associated with xenophagic processing, whereas histone deacetylase 6 (HDAC6) has been implicated in the autophagic processing of protein aggregates and of cilia.

Autophagy may play a complex role in the lung, where it can have both protective and injurious effects on the progression of COPD. At present, there is no unifying explanation for the discrepancies between various studies. The timing and lung cell targets for autophagy may be essential to define its beneficial and pathologic roles in a context-specific manner. A better understanding of the balance between the cytoprotective and pro-death functions of autophagy in response to CS will be required for the therapeutic targeting of this process in COPD.

Pulmonary Hypertension

Pulmonary hypertension (PH) refers to elevated pulmonary arterial pressure that can represent a progressive, fatal disease if untreated (21). Hypoxia causes secondary PH, and hypoxic PH is a progressive and often fatal complication of chronic lung disease (22). We have demonstrated the elevated occurrence of autophagy in lung tissue from patients with PH (23). Mice genetically deficient in LC3B were subjected to chronic hypoxia for determination of the involvement of autophagy proteins in PH and their impact on measured indices of PH. Hypoxic lung tissues displayed increased autophagic vacuoles compared with lung tissue from normoxic mice. After chronic hypoxia, $LC3B^{-/-}$ mice showed increased indices of PH, right ventricular systolic pressure and Fulton's index, relative to wild-type mice. These results suggest that the autophagy protein LC3B may perform a protective function during the pathogenesis of hypoxic pulmonary hypertension.

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease that predominantly affects older patients and has a death rate worse than that of many cancers. However, therapeutic options to alter the course of this disease remain lacking (24). Lung tissues from patients with IPF showed decreased autophagic activity as assessed by LC3B-II expression and few or no autophagosomes by electron microscopy (25). Insufficient autophagy may accelerate cellular senescence in epithelial cells and potentiate myofibroblast differentiation (26). To evaluate the role of autophagy in bleomycin-induced experimental fibrosis, mice were given oral administration of rapamycin, an inducer of autophagy (20). Mice receiving rapamycin in addition to bleomycin displayed significantly lower levels of lung hydroxyproline as a measure of collagen content than mice treated with bleomycin alone. These results suggest that regulating autophagy might alter the course of experimental IPF.

Selective Autophagy: Mitophagy and Ciliophagy in Experimental and Human Lung Disease

Chronic Obstructive Pulmonary Disease

Selective autophagy pathways deliver a wide range of cargo to the lysosome for degradation, including protein aggregates, whole organelles (e.g., mitochondria), and intracellular pathogens (27). Ubiquitin (Ub)-positive substrates, such as protein aggregates (inclusion bodies),

mitochondria, and invading bacteria not dealt with by the proteasome system are selectively degraded by autophagy, suggesting ubiquitination is general tag for selective autophagy (28, 29). Autophagy receptors, such as p62 and neighbor of BRCA1 gene 1 (NBR1), which simultaneously bind monoubiquitinated or polyubiquitinated substrates, act as adaptors between ubiquitination and autophagy (30). Recently, we have demonstrated that mitophagy regulates programmed necroptosis, also called necroptosis, which contributes to the pathogenesis of COPD (Figure 3) (3). CSE, an *in vitro* model of CS exposure, caused significant mitochondrial depolarization and induced mitophagy in lung epithelial cells. We demonstrated that the mitochondrial division/mitophagy inhibitor Mdivi-1 protected against CS-induced cell death by reducing the phosphorylation of mixed lineage kinase domain-like protein (MLKL), a substrate for the receptor-interacting serine/threonine-protein kinase 3 (RIP3) in the necroptosis pathway. Mice genetically deficient in the mitophagy regulator PINK1 were protected against mitochondrial dysfunction, airspace enlargement, and mucociliary clearance disruption during CS exposure. Our results suggest that CS-activated mitophagy may alter mitochondrial membrane integrity and lead to the induction of mitophagy and necroptosis in pulmonary epithelial cells. Moreover, recent studies have suggested that CS-induced mitophagy may regulate cellular senescence in COPD pathogenesis (5). Genetically blocking mitophagy resulted in enhanced CS-induced mitochondrial reactive oxygen species (ROS) production and cellular senescence in HBEC. A precise mechanism by which mitophagy regulates the relationship between necroptosis and senescence remains obscure; however, one possible hypothesis is that mitophagy may lead to either senescence or necroptosis depending on the degree of cellular injury (5).

We also reported that ciliophagy, the consumption of cilia components by autophagy, regulates cilia length during CS exposure (4). We showed that autophagy-impaired (*Becn1*$^{+/-}$ or *Map1lc3B*$^{-/-}$) mice, as well as tracheal epithelial cells isolated from these mice, display a reduction of CS-induced cilia shortening. We identified the cytosolic deacetylase histone deacetylase 6 (HDAC6) as a critical regulator of autophagy-mediated cilia shortening during CS exposure. Importantly, analysis of human COPD specimens demonstrated epigenetic deregulation of HDAC6 by hypomethylation and increased protein expression in the airways. These data suggest that ciliophagy, an HDAC6-dependent

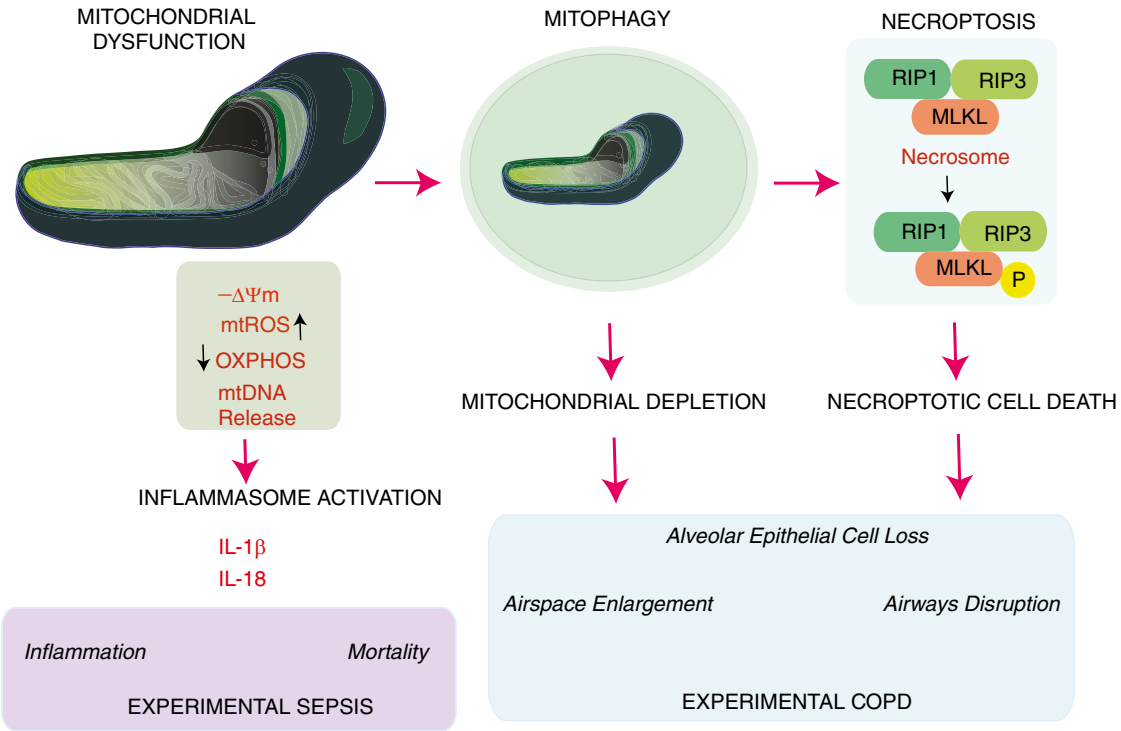

Figure 3. Significance of mitochondrial dysfunction in human disease pathogenesis. Mitochondria have been implicated in the pathogenesis of human disease. Mitochondrial dysfunction associated with depolarization of $-\Delta\Psi$, increased mitochondrial ROS (mtROS) production, decline in oxidative phosphorylation (OXPHOS) and energy charge, and increased release of mitochondrial DNA (mtDNA) has been linked to pathogenic processes. In human sepsis models, mitochondrial dysfunction associated with mtDNA release leads to activation of the inflammasome and secretion of proinflammatory cytokines (IL-1β, IL-18). These events may be associated with sepsis mortality and increased inflammation. In chronic obstructive pulmonary disease (COPD) models, mitochondrial dysfunction was associated with activation of the mitophagy program and subsequent activation of the necroptosis mode of cell death. Necroptosis is regulated by formation of the receptor-interacting serine/threonine-protein kinase (RIP)1/RIP3-containing necrosome, which activates (phosphorylates) mixed lineage kinase domain-like protein (MLKL). These phenomena were linked to increased airspace enlargement, airways dysfunction, and epithelial cell loss in COPD.

selective autophagy pathway, may represent a novel pathway that is critical to cilia homeostasis in response to CS exposure.

It remains to be elucidated how cells use "nonselective autophagy" and "selective autophagy" pathways in response to CS exposure. The term "nonselective autophagy" refers to bulk degradation of cytosol and is implicated as a survival mechanism in starvation. Emerging studies, however, implicate that most substrate degradation by autophagy is assisted by selective processes. We speculate that CS induces nonselective autophagy coincident with injury to organelles (e.g., mitochondria, cilia). Thus, nonselective autophagy and selective autophagy may likely proceed simultaneously in a single cell. In addition, either process may be impacted by cell type and stimulus intensity. Future studies are needed for understanding the relationship between nonselective autophagy and selective autophagy in responses to CS exposure.

Pulmonary Fibrosis

Along with Bueno and colleagues, we have demonstrated that the lungs of patients with IPF exhibit marked accumulation of damaged mitochondria (31, 32). In lung epithelial cells, genetic deficiency of the mitophagy regulator PINK1 potentiated transforming growth factor-β–induced mitochondrial ROS production and cell death (32). PINK1 overexpression also ameliorated endoplasmic reticulum stress–induced mitochondrial accumulation and depolarization (31). Moreover, *Pink1*$^{-/-}$ mice were more susceptible than control mice to bleomycin-induced lung fibrosis (32). These data suggest that induction of mitophagy may improve mitochondrial function in the lungs of patients with IPF. Therapeutic targeting of mitophagy pathway may be useful in the treatment of fibrotic lung diseases.

Autophagy: A Critical Regulator of Cell Death

Basal autophagy is considered as a cellular protective mechanism to degrade cytoplasmic materials and provide energy for cellular renovation and homeostasis (1). Autophagy has also been considered as a suicidal mechanism, and the term "autophagic cell death" was used to indicate instances of cell death associated with excessive cytoplasmic vacuolization (33). However, "autophagic cell death" is not currently recognized as a distinct form of programmed cell death, but rather autophagy can be regarded as a phenomenon commonly associated with cell death pathways (34). In contrast, a previous study suggested that treatment with zVAD, a pan-caspase inhibitor with broad specificity, induced autophagy and the death of L929 cells. This process required RIP1, suggesting that autophagy is involved in necroptosis (35). Subsequently, autophagy has been shown to regulate necroptosis in several models. In childhood acute lymphoblastic leukemia cells, the induction of autophagy-dependent necroptosis was required to overcome glucocorticoid resistance (36). In endothelial cells, the inhibition of autophagy rescued palmitic acid–induced necroptosis (37). Moreover, apoptosis can occur at the same time as autophagy, suggesting a common regulatory mechanism (38, 39). Several studies indicated that proapoptotic signaling molecules induce autophagy, including tumor necrosis factor (40), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (41), Fas-associated protein with death domain (FADD) (42), dynamin-related protein-1 (DRP-1) (43), and death-associated protein kinase (DAPK) (44). In the CS exposure model, we observed reduced epithelial apoptosis coincident with Beclin1 or LC3B knockdown (7, 12). Therefore, an emerging hypothesis is that autophagy proteins can regulate programmed cell death, and vice versa, including necroptosis and apoptosis in a context-specific fashion. We have described that autophagy and selective autophagy can regulate apoptosis and necroptosis in COPD. We demonstrated that dynamic interactions of the autophagic protein LC3B with Cav-1 and Fas regulate CS-induced lung epithelial cell apoptosis, leading to emphysematous airspace enlargement (7). More recently, we also demonstrated that CS-induced mitophagy may alter mitochondrial membrane integrity and lead to the induction of necroptosis (3). However, the precise mechanisms by which mitophagy can aggravate mitochondrial injury or alter mitochondrial dynamics or biogenesis in the CS exposure model remain unclear. Moreover, as dose-dependent effects of autophagy/mitophagy have been proposed, we cannot completely exclude the possibility that autophagy/mitophagy may also contribute to mitochondrial quality control in a prosurvival role during mild CS exposure (45, 46). Further studies are necessary to improve the understanding of the relationship between autophagy/mitophagy and programmed cell death.

Autophagy: A Critical Regulator of Inflammasomes

Sepsis

Autophagy has been implicated in the regulation of inflammation, in particular the regulation of the inflammasome, an inflammatory signaling platform for the secretion of IL-1β and IL-18. Consistent with the findings of Zhou and colleagues, we have revealed that autophagy maintains mitochondrial integrity and prevents damaged ROS-producing mitochondria from activating inflammasome complexes (9, 10). The NLRP3 inflammasome and mitochondrial ROS production regulate cytosolic translocation of mitochondrial DNA (mtDNA) in macrophages, which in turn regulate the secretion of IL-1β and IL-18 (Figure 3). We found that depletion of autophagy proteins promoted the accumulation of dysfunctional mitochondria and increased the cytosolic translocation of mtDNA in response to LPS and ATP stimulation in macrophages (9). Furthermore, we evaluated the function of autophagy in severe sepsis using endotoxemia, commonly used as a model of septic shock, and cecal ligation and puncture (CLP), a more clinically relevant model of polymicrobial sepsis. Mice genetically deficient in LC3B were more susceptible to both LPS- and CLP-induced lethality than control mice. Serum concentrations of IL-1β and IL-18 were significantly higher in endotoxemic *LC3B*$^{-/-}$ mice than in their wild-type littermates (9). These data suggest that autophagy may regulate inflammasome activity by preventing cytosolic translocation of mtDNA commonly associated with severe sepsis, implicating that autophagy has beneficial antiinflammatory effects. Similarly, *Becn1*$^{+/-}$ mice were more susceptible to CLP-induced sepsis. Recently, we have reported that carbon monoxide (CO) confers protection in sepsis by

enhancing Beclin1-dependent autophagy and phagocytosis (47). Although CO enhanced bacterial phagocytosis in mice, this effect was reduced in *Becn1*$^{+/-}$ mice. These results suggest that CO gas may induce xenophagy and phagocytosis, representing a novel therapy for patients with sepsis.

Translational/Clinical Implications

Previously we showed that circulating IL-1β and IL-18 levels increased in critically ill patients with both sepsis and adult respiratory distress syndrome and that increases in circulating IL-18 correlated with disease severity and mortality (48). Consistent with our experimental verification that mtDNA is implicated in inflammasome activity, we also demonstrated that increased mtDNA levels in plasma are associated with intensive care unit mortality and that inclusion of mtDNA level improves risk prediction in medical intensive care unit patients (9). These data suggest that the evaluation of inflammasome activity, including measurements of IL-18 and circulating cell-free mtDNA levels, could provide new diagnostic and/or therapeutic approaches for patients with critical illness.

Conclusions

Accumulating evidence demonstrates that autophagy and selective autophagy exert previously unknown functions during the pathogenesis of human lung diseases. It is now clear that autophagy plays a complex role in the lung, where it can have both protective and injurious effects on the progression of lung disease. Careful consideration and further research are needed for the design of strategies to manipulate autophagy as a valid therapeutic intervention. ■

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

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