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REVIEW

Role and mechanisms of autophagy in lung metabolism and repair

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Abstract

Mammalian lungs are metabolically active organs that frequently encounter environmental insults. Stress responses elicit protective autophagy in epithelial barrier cells and the supportive niche. Autophagy promotes the recycling of damaged intracellular organelles, denatured proteins, and other biological macromolecules for reuse as components required for lung cell survival. Autophagy, usually induced by metabolic defects, regulates cellular metabolism. Autophagy is a major adaptive response that protects cells and organisms from injury. Endogenous region-specific stem/progenitor cell populations are found in lung tissue, which are responsible for epithelial repair after lung damage. Additionally, glucose and fatty acid metabolism is altered in lung stem/progenitor cells in response to injury-related lung fibrosis. Autophagy deregulation has been observed to be involved in the development and progression of other respiratory diseases. This review explores the role and mechanisms of autophagy in regulating lung metabolism and epithelial repair.

Keywords Lung regeneration · Asthma · Idiopathic pulmonary fibrosis · COPD · Glycolysis · Epithelial stem cells

Introduction

The lungs mediate gas exchange between the body and external environment through respiration, which is essential for maintaining life activities. The lungs are metabolically active, and energy consumption is essential for performing routine cellular activities (such as gene transcription, protein translation, and DNA repair) and maintaining the unique activities of the organ, including cilia movement, constriction of the airways and blood vessels, and surfactant production [1]. Glucose, fatty acid, and amino acid metabolisms are the main cellular-metabolic pathways that occur in lung tissue. Autophagy is initiated as a metabolic recycling process in response to nutrition deficiency [2]. Autophagy provides an internal source of glucose, fatty acids, amino acids, and nucleosides that are released for cell metabolic reutilization [3]. Although the basal level of autophagy is low in most tissues, a stressed state greatly stimulates autophagy [4–6]. Data from previous studies showed that metabolic homeostasis plays important roles in regulating cell proliferation and differentiation [7]. Conversely, autophagy controls the cellular energy balance. Increasing evidence suggests that autophagic regulation of energy metabolism is important for lung homeostasis and diseases such as lung cancer, chronic obstructive pulmonary disease (COPD), asthma and pulmonary fibrosis [8, 9]. To maintain normal respiratory function, mammalian lungs have evolved sophisticated injury repair mechanisms. Multiple region-specific epithelial stem/progenitor cells exist in the lung, such as airway stem/progenitor cells [10–14] and alveolar stem/progenitor cells [15–20], which can regenerate and repair the lung epithelium in response to various injuries. In this review, we summarize the role and mechanisms of autophagy in regulating lung metabolism and epithelial repair after lung injury. Autophagy mainly includes three types: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy [21, 22]. We focused on macro-autophagy (hereafter collectively referred to as "autophagy"), which is most commonly studied in the lung.

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Autophagy

Autophagy is a "self-eating" phenomenon that promotes cell homeostasis and organelle renewal through lysosomal mechanisms. The autophagy process involves a series of molecular events, including initiation, elongation, and maturation. Following autophagy-induction signaling, a flat "liposome"-like membrane envelops part of the cytoplasm, cell organelles, and proteins that are targeted for degradation and forms autophagosomes. Next, autophagosomes and lysosomes fuse to form the autophagy–lysosome compartment, after which the contents are degraded and the products are transported to the cytoplasm for reuse or discharged outside the cell [22, 23]. Since the early 1990s, Yoshinori Ohsumi's team and other groups have identified most of the relevant genes involved in autophagy [24], which are known as autophagy-related genes (ATGs) [25, 26]. Among them, two types of proteins are often used as autophagy indicators. Beclin-1 (ATG6) is an important regulatory factor of autophagy, and a change in the ratio of LC3-II/I is an important indicator of the autophagy level [27]. Mammalian target of rapamycin inhibition or AMP-activated protein kinase activation provokes autophagy by stimulating biogenesis of the phagophore membrane [28]. ATG5–ATG12 complexes and LC3-II participate in the autophagosome-formation process [29].

Autophagy is a very "conserved" process that has undergone little evolution. Autophagy is generally considered as a defense and stress-regulation mechanism. Under normal physiological conditions, autophagy occurs at a basal level to maintain cell homeostasis [30]. Autophagy prevents dysfunctional cells from aging and apoptosis, and maintains normal cell physiological functions by removing waste materials from cells [31]. Through autophagy, cells recycle damaged organelles, denatured proteins, and other biological macromolecules. Therefore, autophagy provides the necessary raw materials for cell reconstruction and regeneration [32]. Autophagic flux is typically activated during different types of cellular stress, such as nutrient deficiency, and is visualized by the accumulation of autophagosomes [33]. Autophagy is involved in regulating multiple biological functions, such as inflammation, DNA-damage repair, redox balance, and apoptosis in the lung. Autophagy plays a vital role in maintaining a dynamic balance in the intracellular environment and acts as a homeostatic response to extracellular metabolic stress.

Cellular metabolism in the lung

Cellular metabolism is a general term for a series of ordered chemical reactions that sustain life and includes catabolism and anabolism. Catabolism is the process by which the body breaks down macromolecular substances to obtain energy, and anabolism uses energy to synthesize proteins, nucleic acids, and other macromolecular substances required for various cellular activities [34]. Although cellular metabolism is often discussed in the context of a single pathway, the survival of an organism is ultimately dependent on the integration of all metabolic pathways [1]. Energy consumption in the lungs is essential, both for regulating general cellular functions and for maintaining the unique activities of the organ. Research related to cellular metabolism in respiratory medicine has increased rapidly in recent years. These studies not only provided insight into the complexity of the lungs, but also revealed how changes in cellular metabolism lead to complex pathological events, such as abnormal cilia beating [35], anti-apoptotic behaviors of pulmonary endothelial cells [36], phenotypic polarization of alveolar macrophages, and cellular senescence of alveolar epithelium tissue [37, 38].

Glucose catabolism, pentose-phosphate pathway, and the TCA cycle

Glucose is the main source of energy in most tissues, including the lung. Glycolysis is the energy-production process by which glucose is broken down to produce lactic acid during hypoxia. Glycolysis results in the conversion of one molecule of glucose to two molecules of lactic acid, along with the production of two molecules of ATP. It has been proposed that lactate production serves as a main energy source for cells lacking nutrients in pulmonary circulation [39]. Three irreversible reactions occur in the glycolytic pathway, namely the reactions catalyzed by hexokinase (glucokinase), 6-phosphofructokinase 1, and pyruvate kinase [40, 41]. The pentose-phosphate pathway (PPP) is responsible for oxidative decomposition of glucose and the parallel production of important molecules, such as NADPH and 5-phosphate ribose [42]. PPP is generally activated when lung epithelial cells are exposed to oxidant molecules. Indeed, it has been estimated that over 10% of metabolized glucose is delivered to the PPP for further breakdown in rat lungs [43, 44]. NADPH acts as a key biological reducing agent for various cellular reactions, such as glutathione regeneration, and cholesterol and fatty acid production [43]. Ribose 5-phosphate is the constituent sugar used to synthesize all ribonucleotides. This makes PPP an essential metabolic pathway for cellular proliferation (Fig. 1). Aerobic oxidation of glucose generates pyruvate, which mobilizes to mitochondria for further oxidization to acetyl-coenzyme A, which is completely oxidized to water, carbon dioxide, and ATP through the tricarboxylic acid (TCA) cycle [45] (Fig. 1). The lung is a delicate organ with a large surface area exposed to the external

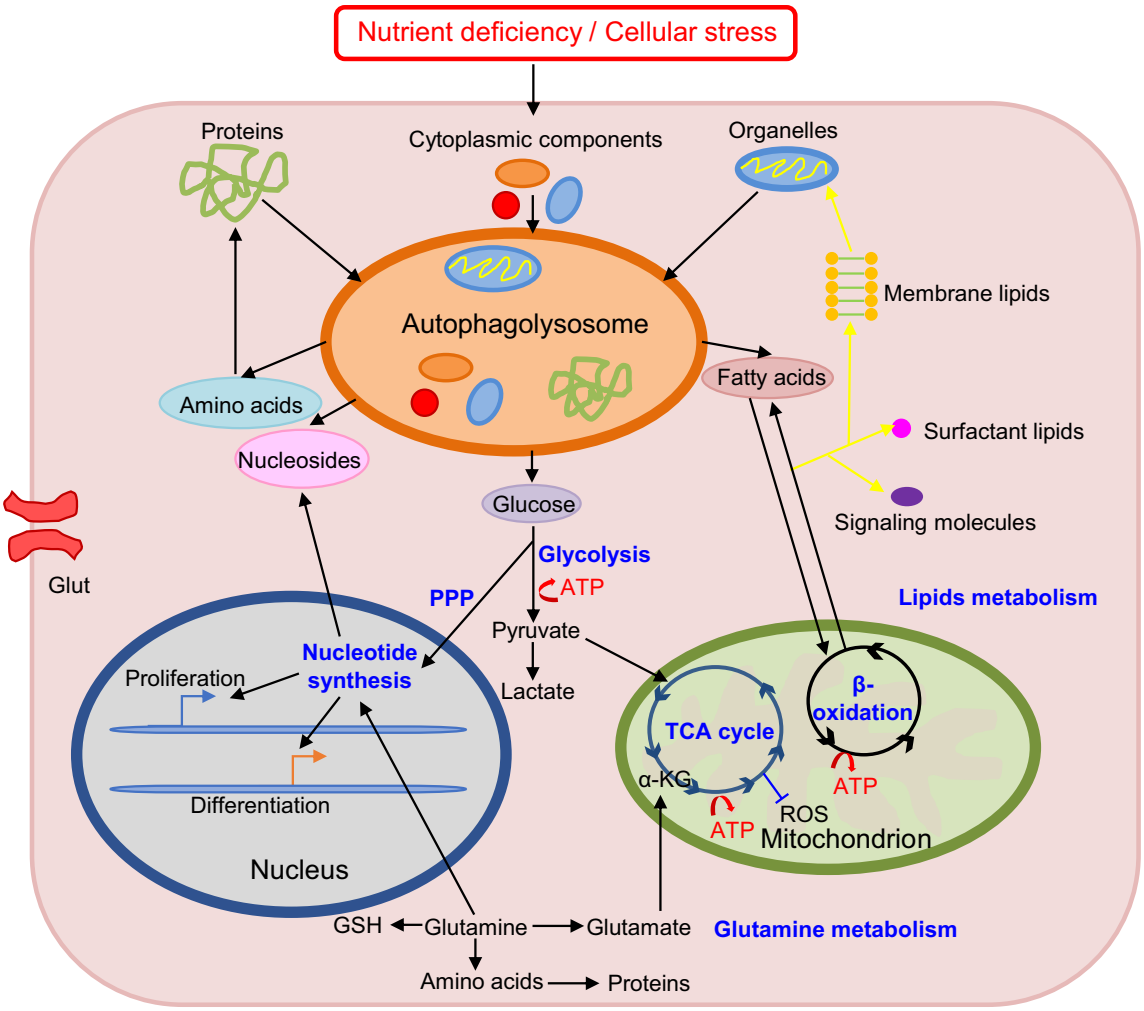

Fig. 1 Autophagy and metabolism in lung tissue. Autophagy is activated in response to nutrient deficiency or cellular stress. After autophagy degradation, glucose, amino acids, fatty acids, and nucleosides are recycled through metabolic reprogramming. *ATP* Adenosine-triphosphate, *α-KG* α-ketoglutarate, *PPP* pentose-phosphate pathway, *ROS* reactive oxygen species, *TCA* tricarboxylic acid cycle

environment, making it highly vulnerable to oxidative stress damage. Inhibiting ATP production through the TCA cycle, but not glycolysis, was shown to enhance reactive oxygen species (ROS) production in lung epithelial cells [46]. ROS can oxidize DNA, proteins, and lipids, resulting in epithelial cell injury in the lung [47].

Lipid metabolism

β-Oxidation is a predominant catabolic process occurring in the mitochondrial matrix, which yields acetyl-coenzyme A and NADH/$FADH_2$ for ATP production [48]. Previous data showed that β-oxidation of fatty acids was upregulated by nearly 40% in the rat lungs during starvation [49]. Although β-oxidation is an excellent source of ATP, it also causes significant oxidative stress to cells. Fatty acid synthesis produces palmitate, phospholipids, triglycerides, and other fatty acid molecules with important roles in energy storage, membrane formation, and signal transduction [50] (Fig. 1). Lipid production is an energy-consuming process, and thus the fatty acid-synthesis pathway is closely related to the energy state of the cell. Alveolar type-II epithelial cells (AT2 cells) are mostly responsible for producing pulmonary surfactants; therefore, they must continue lipid production to reduce alveolar surface tension, even during starvation. AT2 cells have evolved to consume less energy when replenishing their surfactant lipid pools [51]. In addition, lipids are important components of cellular signal-transduction, helping to regulate lung inflammation. As a short-range messenger, eicosanoids are effective biological signal molecules. Arachidonic acid, a 20-carbon fatty acid, is the precursor of many signaling lipid molecules [34]. Prostanoids are metabolites of arachidonic acid [52] and their levels are upregulated in respiratory secretions of patients with COPD,

causing increased inflammation in the lung [53, 54]. Leukotriene B4 is a potent lipid mediator of inflammation and is related to various inflammatory diseases including asthma and COPD [55, 56].

Glutamine metabolism

In addition to glucose and lipids, glutamine (Gln) metabolism (which produces α-ketoglutarate in the TCA cycle) and amino acid and nucleotide synthesis are essential for maintaining cellular homeostasis. Gln is deaminated by glutaminase to form glutamate, an important intermediate metabolite for amino synthesis [57]. Glutamate is a precursor of the main cellular antioxidant, glutathione. In addition, Gln metabolism is a source of non-essential amino acids that are required for macromolecular synthesis (Fig. 1). Previous results suggested that Gln is necessary for myofibroblast differentiation and collagen production [58–60]. Maintenance of bodily Gln homeostasis requires a balance between Gln release and uptake in the body. Recent data suggested that lungs play important roles in Gln flow under both normal and catabolic states [61]. The lungs express Gln synthetase l, which catalyzes de novo Gln synthesis [62]. During physiological stress, the lungs increase production of the amino acid glutamine to maintain Gln homeostasis [63]. Respiratory diseases are often accompanied by enhanced inflammatory responses and catabolic activity. Under these conditions, changes occur in terms of Gln concentration and depletion. Exogenous Gln administration may be beneficial for inhibiting respiratory diseases, particularly in individuals with asthma or lung cancer [64]. Further studies are necessary to clarify the regulation of lung Gln levels at the whole-organ and cellular levels.

Regulation of lung metabolism by autophagy

Autophagy is activated in response to the deprivation of nutrients, such as amino acids or glucose [65, 66]. During starvation, hexokinase II, the first mediator of glycolysis, promotes autophagy and glucose metabolism to maintain survival [66]. After autophagy-based degradation, glucose, fatty acids, amino acids, and nucleosides are reused in lung metabolic processes (Fig. 1). Autophagy facilitates glucose uptake and lactate production by promoting plasma membrane translocation of glucose transporter 1 (Glut1) in hypoxic cells [67]. In airway Club cells, autophagy may enhance glucose uptake through Glut1 trafficking, rather than by increasing Glut1 expression [68]. In AT2 cells, autophagy reprograms metabolic pathways by promoting glucose metabolism while inhibiting fatty acid metabolism [69]. Autophagy-deficient lung tumor cells are dependent on fatty acid oxidation for energy production [70]. Autophagy regulates β-oxidation and ketone body production during fasting [71]. Recent evidence suggested that lipid droplets act as direct lipid sources for autophagy and that lack of lipid droplets may inhibit autophagy [72]. Non-small cell lung cancer cells lacking Atg7 were more sensitive to starvation, which was reversed by exogenous Gln [73]. Gln metabolism restores autophagy-dependent mammalian target of rapamycin C1 activation in case of amino acid starvation in mouse embryonic fibroblasts [74]. Undoubtedly, autophagy regulates lung tissue metabolism, and metabolism has a profound impact on autophagy. Autophagy is a metabolic process that controls either the airway or alveolar cell energy balance. Increasing evidence indicates that autophagy plays vital roles in regulating energy metabolism during respiratory diseases. It is important to further understand the metabolic changes caused by autophagy and to study the reuse of the metabolic substrates produced by autophagy in the lung tissue.

Lung epithelial stem/progenitor cells and tissue regeneration

Efficient lung repair relies on healthy epithelial stem/progenitor cells, which exhibit region-specific distributions and responses to various lung injuries. The large airways (trachea and bronchi) are covered with a layer of pseudostratified columnar epithelium, which contains basal, goblet, ciliated, and Club cells. These cells are scattered by submucosal glands. Secretory, goblet, and Club cells secrete various mucins, which are the main components of mucus covering the airway epithelium [75]. The cell populations in the small airway (bronchioles and terminal bronchioles) include Club cells, ciliated cells, neuroendocrine cells, and a small number of basal cells [76]. To maintain normal function, the lung airway epithelium employs multiple repair mechanisms in the steady state or under conditions of severe damage. There are multiple subtypes of basal cells, and keratin 5^+ ($Krt5^+$) basal cells can differentiate into Club cells and ciliated cells. $Krt5^+$ basal cells express the transcription factor p63, which functions to help maintain a stable number of basal cells [77]. After tracheal epithelial injury, stromal cells secrete interleukin (IL)-6 to promote the differentiation of $p63^+Krt5^+$ basal cells into ciliated cells [78]. Previous data suggested that in response to H1N1 influenza A virus infection, rare distal airway stem cells expressing p63 and Krt5 underwent proliferative expansion and differentiated into nascent alveolar epithelial cells [76]. Pulmonary neuroendocrine cells expressing calcitonin gene-related peptide [79] can proliferate and differentiate into Club cells and ciliated cells [80]. Club cells show a self-renewal ability and can differentiate into ciliated cells and goblet cells [81, 82]. They also participate in xenobiotic metabolism by expressing cytochrome p450 and regulate lung inflammation by secreting Club cell secretory protein (CCSP). When naphthalene

injury causes Club cell loss, variant Club (vClub) cells expressing lower levels of Scgb1a1 can replenish the Club cell population [83, 84]. Using hereditary mice, our previous studies revealed subtypes of Club cells in the mouse airways, which could promote regional epithelial cell repair [14]. We found that the airway progenitor cells (vClub and Club) were essential for epithelial repair during ovalbumin-induced acute inflammation.

The alveolar epithelial mucosa is connected to the terminal bronchioles, serving as an important barrier, and the pulmonary alveolar epithelium plays important roles in the lungs by promoting gas exchange-dependent host defenses [85]. The alveolar epithelium is comprised of alveolar type 1 (AT1) and alveolar type 2 (AT2) cells [86]. AT1 cells are flat and abundant, accounting for approximately 95% of the alveolar surface area, and form a very thin gas-exchange surface as an air–blood barrier. AT2 cells synthesize and secrete various surfactants that can not only reduce alveolar surface tension, but also have antioxidant and antibacterial effects [87, 88]. AT1 and AT2 cells are tightly connected to each other to maintain the integrity of the alveolar epithelia [89, 90]. Several types of stem/progenitor cells exist and are capable of repairing the adult alveolar epithelium in response to injuries [13, 91–93]. Previous data showed that AT2 cells proliferate and give rise to AT1 cells to restore the alveolar epithelium during bleomycin injury [15, 18, 19], and thus the cells are considered as alveolar stem/progenitor cells [15, 94]. In addition, a subset of alveolar cells expressing the laminin receptor α6β4 but no surfactant protein C can regenerate AT2 cells following bleomycin-induced lung injury [11]. Lineage-negative progenitor cells mobilize to regenerate the alveolar epithelium after bleomycin- or influenza-induced injury in mice [12]. In addition, Kim et al. identified cells expressing both scgb1a1 and surfactant protein C in the terminal bronchioles of mice, which were designated as bronchioalveolar stem cells (BASCs) [10, 19]. BASCs are resistant to alveolar damage and proliferate after bleomycin treatment [10, 95]. Additionally, epithelial cells with CCSP-promoter activity, but not CCSP expression, are observed in the alveolar space and participate in alveolar development [96]. Adult AT1 cells that were lineage-labeled with the atypical homeodomain-containing protein Hopx proliferated and gave rise to AT2 cells during adult alveolar regrowth following partial pneumonectomy [16, 17]. The AT1 cell population contains $Hopx^{+}$ $Igfbp2^{+}$ and $Hopx^{+}$ Igfbp2-subsets, which have different cell fates during alveolar epithelial regeneration. $Hopx^{+}$ $Igfbp2^{+}$ AT1 cells are terminally differentiated and cannot transdifferentiate into AT2 cells after pneumonectomy [17]. Together, these data suggest that alveolar stem/progenitor cells respond to injuries within the lung epithelium and contribute to subsequent regeneration of the lung.

Autophagy in stem cell metabolism and regeneration in lung diseases

Lung tissue is metabolically active, and energy consumption is not only essential for regulating cell function but also essential for maintaining respiratory activity. Dysregulation of autophagy and metabolism are associated with many disease processes including metabolic diseases, cancer, and neurodegenerative diseases. In the context of respiratory diseases, current studies have found that autophagy and metabolism are involved in the pathology of lung cancer, chronic obstructive pulmonary disease (COPD), asthma, and idiopathic pulmonary fibrosis (IPF).

Lung cancer

Lung cancer is the primary cause of all cancer-related deaths worldwide [97]. Lung cancers are usually divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The major histological type is non-small cell lung cancer, constituting 80% of all lung cancers, and includes adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma [98]. Despite great advances in the treatment of NSCLC and increasing understanding of tumor progression over the last two decades, the poor prognosis of these tumors urgently warrants further research into the molecular mechanisms of lung tumors and the development of novel therapeutic strategies that are more efficacious [99]. Research has shown that lung cancers may originate from either endogenous stem cells, or from a group of tumorigenic cells called cancer stem cells (CSC) [100]. Improper epithelial regeneration contributes to the development of lung cancer [101].

Lung tumor cells usually initiate autophagy in response to the rapidly increasing need for material and energy substrates. Autophagy has a dual role in promoting apoptosis in NSCLC. On the one hand, autophagy can provide a source of metabolic substances for tumor cells to promote their growth. Inhibition of autophagy causes an imbalance in cellular homeostasis, accelerating its apoptosis. On the other hand, autophagy can stimulate activation of the apoptotic pathway, promoting cell apoptosis [99]. Tumor cells characteristically exhibit significant metabolic alterations when compared to healthy cells. These altered metabolic levels maintain their high proliferation and survival rates, even in an environment of nutrient deficiency and insufficient oxygen [102]. Autophagy is known to promote glycolysis during tumorigenesis [103], increasing glucose uptake by promoting the expression of Glut1 [67]. Cells produce large amounts of lactic acid by anaerobic glycolysis, even in the presence of sufficient oxygen, known as the Warburg effect [41, 104]. Glycolysis serves as an important source

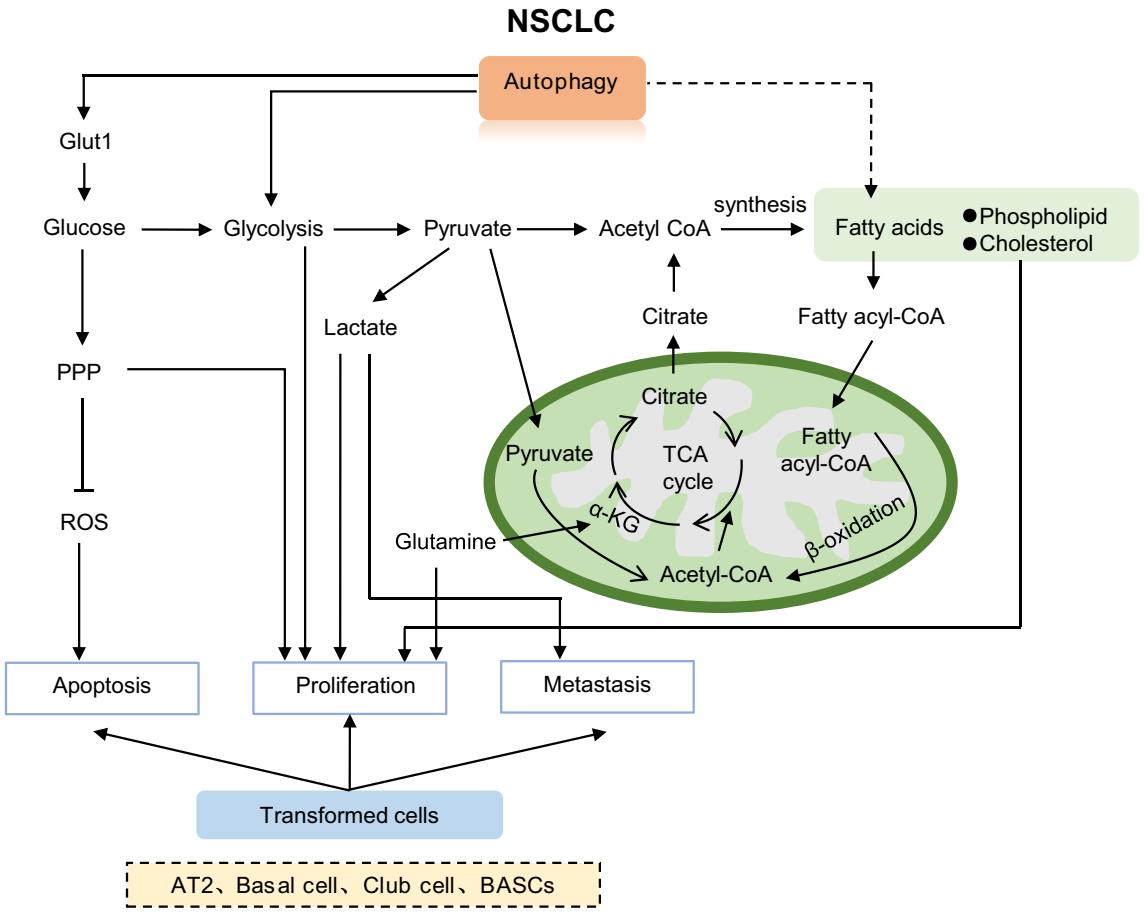

Fig. 2 Regulation of lung repair by autophagy in NSCLC. NSCLC originates from transformation of lung stem/progenitor cells. Lung tumor cells initiate autophagy to meet the energy requirement for rapid proliferation. Autophagy activates glycolysis to provides a source of metabolic substances and sufficient energy for tumor cells to grow. *NSCLC* non-small cell lung cancer, *ROS* reactive oxygen species, *PPP* pentose-phosphate pathway

of intermediates for the synthesis of substances, including lipids, proteins, and nucleic acids, which are essential for cell growth and proliferation [1]. Once pyruvate is formed, it is usually used to either produce acetyl-CoA and enter the mitochondrial metabolism through the tricarboxylic acid (TCA) cycle, or to produce lactic acid through lactate dehydrogenase [1]. Lactic acid can then induce the production of hyaluronic acid, promoting tumor metastasis [104] (Fig. 2). Additionally, lactic acid can induce the secretion of vascular endothelial growth factor (VEGF), promoting the formation of new blood vessels that provide oxygen and nutrients for cell growth and proliferation [104]. Autophagy is significantly elevated in tumor cells, and consequently there is reason to believe that autophagy may promote the proliferation of tumor cells by regulating glycolysis, and producing large amounts of lactic acid. The increase in pyruvate to lactic acid limits the availability of acetyl-CoA required to flow into the TCA cycle. To compensate for this approach, tumor cells increase their uptake of the non-essential amino acid glutamine [102]. High levels of glutamine have been observed in lung cancer, especially in NSCLC, and these elevated glutamine levels support tumor progression [105]. As a source of carbon and nitrogen, glutamine participates in the synthesis of proteins, purine bases, and fatty acids, promoting the proliferation of tumor cells [105]. Moreover, the metabolism of glutamine activates several signaling pathways, such as mTOR and MAPK, to promote tumor cell proliferation [102] (Fig. 2).

In addition to glycolysis and glutamine metabolism, the pentose-phosphate pathway (PPP) is also an important pathway in tumor cell metabolism. The PPP, a branch of glycolysis at the first step of glucose metabolism, is a main source of NADPH and ribonucleotides synthesis [106]. As an important reductant, NADPH can reduce the level of reactive oxygen species (ROS) and inhibit tumor cell apoptosis, while simultaneously participating in the synthesis of cholesterol and fatty acids for cell proliferation [1, 106] (Fig. 2). Notably, autophagy also degrades lipids into fatty acids, providing substrates for the TCA cycle [103].

Levels of lipid metabolism are also significantly elevated in tumor cells. Tumor cells synthesize large amounts of fatty acids, which are essential for cell membrane biosynthesis and signal transduction. Fatty acid synthesis is derived from acetyl-CoA, which is supplied by citrate in the TCA cycle. Phospholipids are major components of cell membranes, and play an important role as secondary messengers in inter- and intracellular signal transduction. For example, phosphatidylinositols (PI) often serve as secondary messengers to activate the AKT pathway in the regulation of cell proliferation in NSCLC. Another important process involved in cancer progression is cholesterol synthesis [107]. Studies have shown that occurrence of lung cancer is related to imbalances in cholesterol metabolism with an important role in the maintenance of cell homeostasis [108]. Cholesterol levels are elevated in tumor cells, contributing to tumor development [109] (Fig. 2).

Metabolic reprogramming plays an important role in the occurrence and development of tumors; elevated metabolic levels promote the growth and proliferation of tumor cells. Autophagy is closely related to tumor cell migration, invasion, tumor stem cell proliferation and differentiation. On the contrary, autophagy promotes the survival of lung cancer cells, which is conductive to the occurrence and development of tumors. Contrarily, autophagy also causes cell apoptosis or death, thereby inhibiting tumor development [110]. Autophagy and metabolism in tumor cells are therefore inextricably linked. The cross-regulation of these processes acts to buffer the proliferation of cancer cells from excessive environmental and internal pressure. A better understanding of how autophagy promotes the metabolism of transformed lung stem/progenitor cells will subsequently provide insights into more effective therapeutic approaches for cancer.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is caused by alterations in airway epithelium, including cilia shortening and goblet cell hyperplasia, and alveolar disruptions including cell apoptosis and senescence [111]. Pathogenesis of COPD was studied with well-established animal models of cigarette smoke (CS) exposure [112]. Stimulation of lung epithelial cells with CS extract or exposure of mice with CS were shown to alter autophagy, however, it is debatable whether autophagy is inhibited or activated during these treatments [113–115]. This discrepancy could result from variations in the cell types analyzed, the complexity of cigarette components, or variations to the duration of CS exposure. It seems clear that autophagy is induced in lung tissue from COPD patients due to increased expression of autophagic proteins [116], however, cell-specific analysis of autophagy in lung tissue from COPD patients remains to be investigated.

In airways, CS was shown to strengthen the PPP metabolic pathway of glucose, which prevents ROS-induced cell senescence of airway epithelial cells [117] (Fig. 3). It is unclear whether this relates to airway epithelial hyperplasia in COPD patients. Glycolysis favors Club cell proliferation, but inhibits goblet cell differentiation and ciliated cell differentiation [68] (Fig. 3). Autophagy facilitates glucose uptake by Club cells and exhibits similar role in regulating Club cell fate, suggesting that autophagy may promote glycolysis [68]. These data suggest that autophagy inhibition abrogates glycolysis-derived goblet cell over-differentiation of Club cells during COPD pathogenesis. However, mucin secretion requires autophagy [118]. Autophagy overactivation is harmful and induces cell apoptosis, while inhibition of autophagy leads to airway epithelial cell senescence [113, 114, 119] (Fig. 3). Fatty acids including cholesterol are important components of the cell membrane, and are therefore required for the proliferation of stem/progenitor cells; oxidative products of cholesterol 25-HC/27-HC are, however, associated with leukocyte activation and inflammation and resulting airway epithelial cell apoptosis and senescence in COPD [120, 121] (Fig. 3). Similarly, glycerol products LTB4 and PGE2 are increased in COPD patients, and LTB4-induced neutrophilic inflammation contributes to airway epithelial cell apoptosis and senescence [122] (Fig. 3). This may explain why fatty acid oxidation is shown to be promoted during CS exposure [123]. Autophagy is impaired by oxidative stress, but long-chain fatty acids induce autophagy [124]. The role of autophagy in regulating lipid oxidation and synthesis in airway stem/progenitor cells remains unclear.

In alveoli, CS extract induces autophagy in AT2 cells [125]. Glycolysis and lactate production are inhibited by CS exposure [126]. This suggested that autophagy may play a different role in alveolar cell fate determination. A recent study indicated that CS-induced senescence of AT2 cells was due to decreased autophagy [127]. Inhibition of autophagy also promotes AT2 cell apoptosis [128] (Fig. 3). AT2 cell apoptosis and senescence contributes to the emphysema observed in COPD patients. Cell apoptosis and senescence mainly due to the action of ROS, which could be prevented by PPP metabolic pathway of glucose. These data suggested that autophagy may promote PPP pathway in AT2 cells in COPD. CS exposure was shown to enhance β-oxidation of phosphatidylcholine, a major surfactant phospholipid [126]. Inhibition of early steps of fatty acid synthesis favors AT2 cell proliferation [69]. These fatty acids cannot be components of the cell membrane. Phospholipid ceramide is able to induce AT2 cell apoptosis [129]. When mitophagy occurs, β-oxidation process of fatty acids that are transported into the mitochondria is terminated. However, it

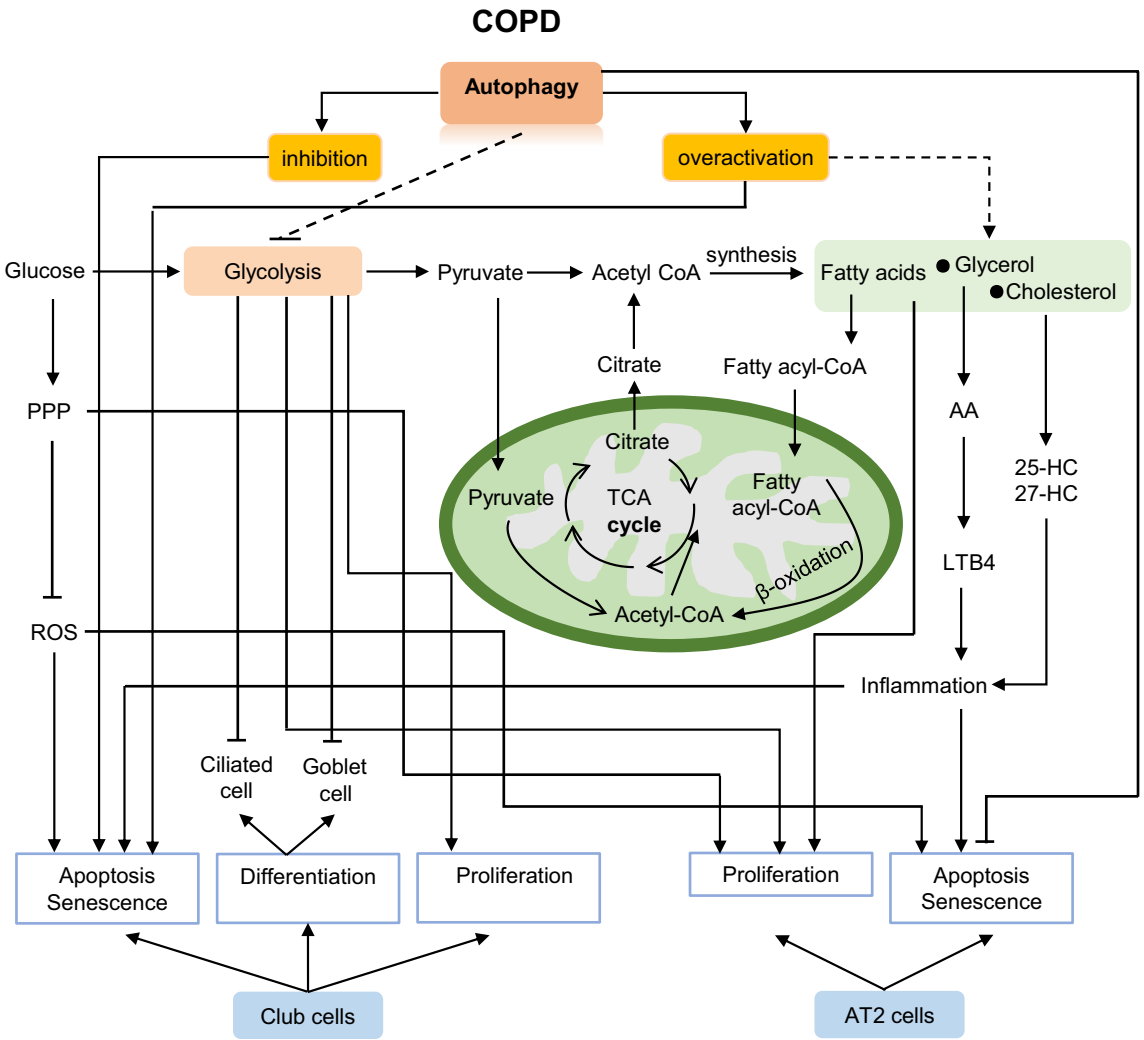

Fig. 3 Regulation of lung repair by autophagy in COPD. In COPD, autophagy inhibition or overreaction leads to cell apoptosis or senescence. Autophagy level impacts the metabolism of glucose and fatty acids. Glycolysis promotes the proliferation of both airway Club cells and alveolar AT2 cells, but inhibits goblet cell differentiation and ciliated cell differentiation. Autophagy prevents ROS-induced AT2 cell apoptosis. Fatty acids promote cell regeneration, but some lipids also accelerate cell senescence and apoptosis by affecting the secretion of inflammatory factors. *AA* arachidonic acid, *25-HC* cholesterol 25-HC, *27-HC* cholesterol 27-HC, *COPD* chronic obstructive pulmonary disease, *LTB4* Leukotriene B4, *ROS* reactive oxygen species, *PPP* pentose-phosphate pathway

was also shown that mitochondria respiration is increased following CS exposure [123]. This suggests that the level of autophagy is essential to regulation of cellular metabolism in COPD. Actually, both lack of autophagy and overaction of autophagy are known to be associated with COPD pathogenesis. Surprisingly, a recent report showed that the stem cell status of AT2 cell is strengthened in response to chronic CS exposure [130]. A comprehensive understanding of the metabolic regulation underlying AT2 cell self-renewal and differentiation is lacking in the field. Overall, autophagy is important in metabolic reprogramming through regulation stem/progenitor cell fate during COPD pathogenesis, but the underlying mechanisms of these regulatory effects are highly complex.

Asthma

Asthma is a chronic airway disease characterized by bronchial inflammation, airway hyperresponsiveness, and airflow obstruction [131]. Airway remodeling in asthma includes epithelial damage, cilial dysfunction, and goblet cell hyperplasia. These features aggravate asthma by thickening the airway wall, secreting mucus, as well as obliterating small airway passages [132]. Recent studies indicated that changes in autophagy levels affect the direction and prognosis of asthma [133]. In bronchial biopsy tissues from moderately severe asthmatic patients, double-membrane autophagosomes were found to be more prevalent in epithelial cells compared to those of healthy controls [134].

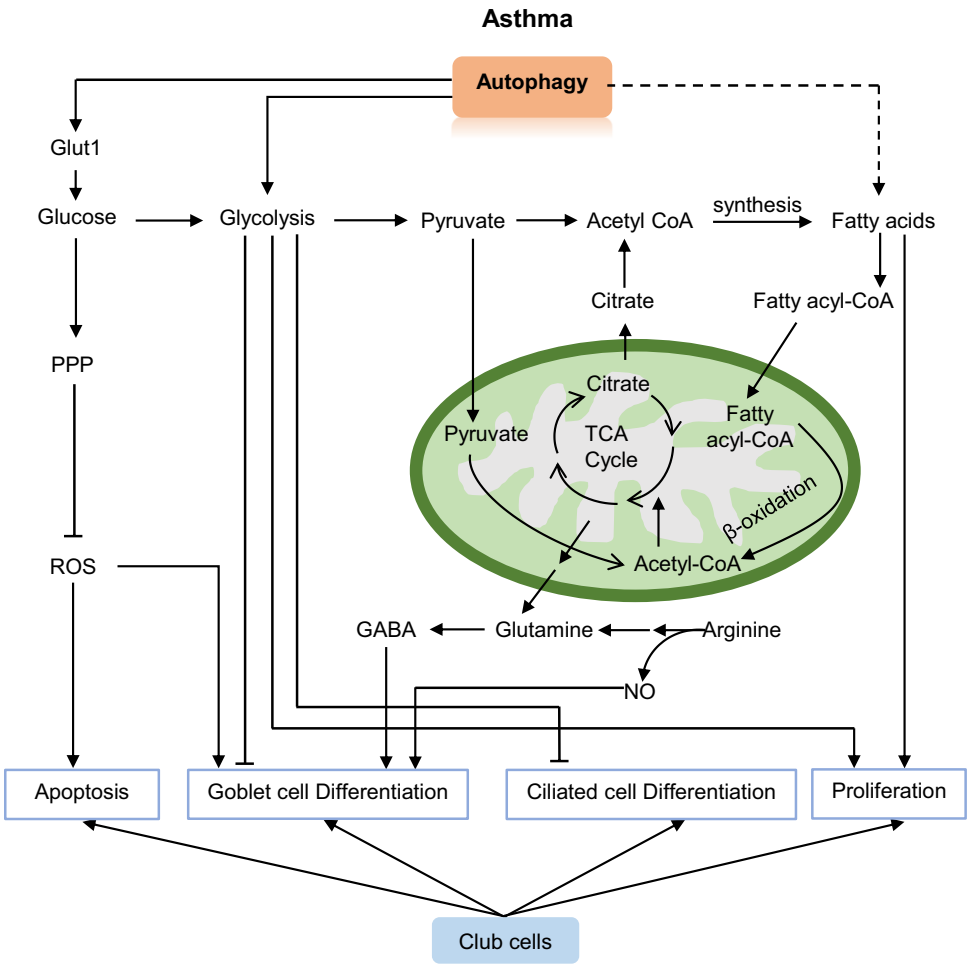

Fig. 4 Regulation of lung repair by autophagy in Asthma. In asthma, autophagy increases the level of glucose metabolism by promoting glucose uptake. Glycolysis promotes the proliferation of Club cells and prevents goblet cell differentiation. Insufficient autophagy in airway progenitor cells may impair airway epithelial repair and promote goblet cell hyperplasia. Both the arginine metabolite NO and the glutamine metabolite GABA promote the mucin secretion of goblet cells. *GABA* γ-aminobutyric acid, *ROS* reactive oxygen species, *PPP* pentose-phosphate pathway

In a mouse model of house dust mite (HDM)-induced allergic airway disease, an increase in glycolysis was observed in lung tissue homogenates during HDM exposure; this finding was also observed in primary nasal epithelial cells (NECs) from asthmatics [135]. Our previous research has found that autophagy promotes the proliferation of vClub and Club cells during ovalbumin-induced acute inflammation. Loss of Atg5 disrupts the uptake of glucose in vClub cells. Glucose deprivation or glycolysis inhibition is not conducive to the proliferation of vClub and Club cells but is beneficial to the differentiation of ciliated and goblet cells [68] (Fig. 4). These results show that autophagy is beneficial for lung epithelial repair in asthma progression. The pentose-phosphate pathway is known to generate NADPH that prevents ROS-induced goblet cell differentiation [136] and epithelial apoptosis, and seems to be an alternative mechanism for autophagic regulation of Club cell fate in asthmatic inflammation (Fig. 4).

There has no evidence on the regulation of fatty acids by autophagy in Club cells. However, many fatty acids are components of the cell surface membrane; it is most likely that autophagy promotes fatty acid synthesis, promoting cell division for cells including airway stem/progenitor cells. It has been reported that fatty acid oxidative decomposition alleviates airway hyperresponsiveness and mucus production [137]. Mucus production and bronchial hyperresponsiveness are both increased in response to mitochondrial oxidative damage [138]. Mitochondrial arginase transports ornithine into the mitochondrion in the asthmatic airway epithelium. In this manner, it supplies nitrogen for the de novo synthesis of arginine to replenish TCA cycle intermediates and for the formation of nitric oxide (NO) through the nitric oxide synthase (NOS) pathway [139]. Disturbance of NO synthesis via competition for L-arginine is responsible for protection against the epithelial shedding that is seen in asthma in turn [140] (Fig. 4). Reportedly, synthesis of spermidine through a pathway involving L-arginine metabolism has been implicated in the facilitation of autophagy [141]. In addition, gama-aminobutyric acid (GABA) produced by pulmonary neuroendocrine cells in mice makes a difference in mucus overproduction [142] (Fig. 4). This may explain the various effects of glutamine metabolism on asthma progression. Although a number of studies have showed that autophagy and metabolism play an important role in the pathogenesis

of asthma, the molecular mechanism of autophagy regulating cell metabolism requires further investigation.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic interstitial pneumonia whose pathogenesis remains poorly understood. It is currently believed that IPF is the result of repeated damage to the alveolar epithelium, dysregulation of cellular homeostasis, abnormal wound healing and insufficient repair of the epithelial injuries. IPF is an age-related disease. It is generally believed that autophagy activity decreases with age, and might lead to the accumulation of damaged macromolecules and organelles in lung tissue [143]. Studies have shown that autophagy flow is blocked and its function is reduced in the lung tissue of patients with IPF. It is characterized by decreased number of autophagosomes, autophagosomes failed to fuse with lysosomes, and the accumulation of p62 and ubiquitinated proteins in the cells [144, 145]. Decreased autophagy in alveolar epithelial cells promotes p21-mediated cellular senescence [146, 147]. Aging lung epithelial cells can release a large amount of profibrotic cytokines and inhibit autophagy, thereby promoting the progression of pulmonary fibrosis [145]. Collectively, these findings indicate that impaired autophagy may contribute to pulmonary fibrosis. However, the molecular mechanism of autophagy deficiency in regulating the development of pulmonary fibrosis remains to be comprehensively elucidated. Annie Pardo et al. have shown that autophagy is activated in the bleomycin-induced pulmonary fibrosis [148–150]. Inhibition of autophagy by an Atg4b deficient mouse model intensified the apoptosis of alveolar epithelial cells and promoted the progression of pulmonary fibrosis [148]. Autophagy is an adaptive survival response, which protects alveolar epithelial cells against senescence and apoptosis in pulmonary fibrosis.

In IPF, oxidative stress, endoplasmic reticulum (ER) stress, and hypoxia are well known as inducers of autophagy [151–156]. Autophagy is also a metabolic process, which regulates cell metabolism to achieve controlling energy balance and maintaining cell homeostasis. Studies have found that glucose anaerobic glycolysis is activated in IPF lung tissue [157], the level of intracellular lactate is increased [158], and TCA cycle enzymes and metabolites are downregulated [158]. Autophagy can promote glucose uptake in lung epithelial cells, thereby increasing the intracellular glucose metabolism process [68]. We speculate that pyruvate produces lactic acid under anaerobic conditions, and the accumulation of large amounts of lactic acid accelerates the apoptosis of alveolar epithelial cells in IPF [159, 160] (Fig. 5). In addition, for stem cells, inhibiting glycolysis and increasing the TCA cycle is conducive to cell differentiation [161, 162]. However, the level of glycolysis is increased while the TCA cycle is decreased in alveolar epithelial cells. This metabolic change is harmful to the differentiation of AT2 [163, 164] (Fig. 5). At the same time, studies have found that the levels of glutamine, glutamate, and GSH are reduced in alveolar epithelial cells [157]. The slow metabolism of glutamine may be due to the stimulation of glucose metabolism by autophagy, which makes the alveolar cells more dependent on glycolysis for energy in IPF. Glutamine is essential for cell proliferation as it provides nitrogen, pyrimidine, and protein for purine biosynthesis [74]. Moreover, glutathione is ROS inhibitor, and the reduction of GSH levels is unfavorable for cell resistance to oxidation stress-induced senescence and apoptosis [165] (Fig. 5). Therefore, the slowing down of glutamine metabolism is not conducive to alveolar cell proliferation and anti-oxidation.

Elevated levels of free fatty acids can induce autophagy, which in turn inhibits further fatty acid synthesis; this may be an important mechanism to avoid lipo-toxicity [69, 166, 167]. Neutral lipid stores are mobilized to support autophagic membrane formation [69]. There are many types of fatty acids, and their mechanisms of regulating cellular functions vary. Studies have shown that the level of palmitic acid is elevated in the lung tissues of patients with IPF [168]. After bleomycin induces pulmonary fibrosis, a high-fat diet rich in palmitic acid causes lung epithelial cell death and pro-apoptotic endoplasmic reticulum (ER) stress response [168, 169] (Fig. 5). However, sphingolipids, as the main component of cell plasma membrane, are closely related to cell proliferation. Studies have shown that levels of sphingosine metabolites are reduced in the lung tissue of IPF patients, which is not conducive to the remodeling of the lung epithelial structure [158]. From this perspective, autophagy inhibits the synthesis of sphingolipids, which is not conducive to the proliferation of alveolar epithelial cells (Fig. 5). Accumulating evidence illustrates there are many dysfunctional mitochondria in the alveolar epithelial cells of IPF lung tissue [170]. Mitochondrial dysfunction impairs the TCA cycle and fatty acid β-oxidation, which provide energy and macromolecules for proliferating cells. In addition, mitochondrial dysfunction induces epithelial cell senescence and apoptosis [171]. Inhibition of the formation of phospholipids and cholesterol prevent AT2 cells from secreting surfactant following mitochondrial dysfunction [172]. Interestingly, autophagy can eliminate dysfunctional mitochondria and prevent cellular senescence and apoptosis [166].

Previously, we reported that the absence of Atg5 from AT2 cells accelerates bleomycin-induced lung injury [69]. In bleomycin-induced lung fibrosis, glucose catabolism is increased, and fatty acid anabolism is decreased in alveolar epithelial cells. When lack of autophagy gene Atg5 in AT2 cells, this metabolic level is reprogrammed, along with decreased abundance and impaired proliferation of AT2

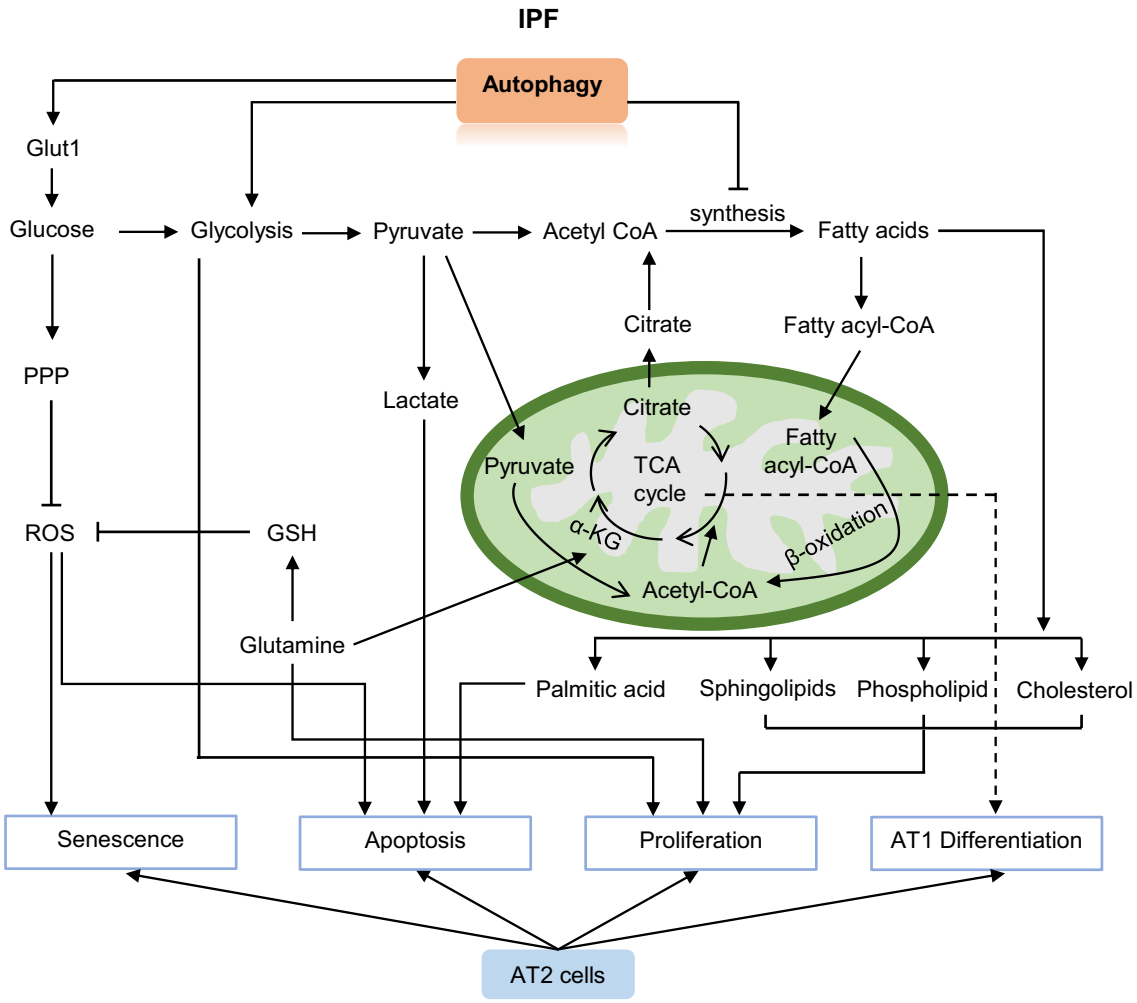

Fig. 5 Regulation of lung repair by autophagy in IPF. Autophagy is activated in AT2 cells in IPF. Autophagy promotes the regeneration of alveolar epithelium by promoting glucose catabolism and inhibiting fatty acid synthesis. Glycolysis accelerates the proliferation of alveolar epithelial cells, and increasing TCA cycle is conductive to AT1 differentiation. Palmitic acid causes lung epithelial cell death, but phospholipids and cholesterol which are the main components of cell membranes and surfactants are necessary for AT2 cell proliferation. *AT1* alveolar type 1, *AT2* alveolar type 2, *IPF* idiopathic pulmonary fibrosis, *GSH* glutathione, *ROS* reactive oxygen species, *PPP* pentose-phosphate pathway

cells. Therefore, we believe that autophagy promotes the regeneration of alveolar epithelium by promoting glucose catabolism and inhibiting fatty acid synthesis. In vitro, inhibition of fatty acid synthase activity can promote the proliferation of AT2 cells, and this effect depends on autophagy. In bleomycin-induced lung injury, loss of Glut1 occurs, while damage to AT2 cells is aggravated and their proliferation is decreased. In addition, inhibiting the hexokinase or pentose-phosphate pathway in glucose metabolism is not conducive to the proliferation of AT2 cells and accelerates the progression of pulmonary fibrosis (Fig. 5). This may be result from anaerobic glycolysis and aerobic oxidation in the process of glucose metabolism producing large amounts of ATP, which is beneficial for cell proliferation and differentiation [163, 164]. NADPH produced by the metabolism of pentose-phosphate pathway resists cellular oxidative stress and prevents alveolar cells from senescence and apoptosis. At the same time, the production of ribonucleic acid facilitates the synthesis of nucleotides and further promotes the regeneration of alveolar cells [42] (Fig. 5). These results indicate that autophagy regulates the metabolic reprogramming of alveolar epithelial cells to meet the energy and substrate requirements for alveolar epithelium regeneration.

Conclusions and perspectives

In summary, although autophagy has been highly conserved during evolution, different mechanisms regulate autophagy in different cells in lung tissues. Accumulating evidence

suggests that autophagy participates in regulating diverse biological functions in the lungs, such as inflammatory responses, DNA-damage repair, apoptosis, cell proliferation, and differentiation. Therefore, autophagy plays a vital role in maintaining metabolic homeostasis in lung tissues and in the development and pathogenesis of chronic respiratory diseases. Additionally, autophagy elicits both protective and injurious effects during the progression of lung disease; these diverse effects may vary with different types of diseases or different cell types in the lungs. More and more evidences also show that autophagy plays an important role in regulating energy metabolism and the development of metabolic diseases. Autophagy causes lung epithelium metabolic reprogramming and regulates the energy balance of metabolic pathways in asthma and bleomycin-induced lung fibrosis. In general, autophagy acts as a regulator, not only in maintaining metabolic homeostasis, but also during lung repair.

However, the role of autophagy in regulating lung regeneration and metabolism is not fully understood. Since autophagy is a dynamic biological process, we need to understand the changes of autophagy activity in specific cell types at different stages of disease development. Significant progress has been made in our understanding of energy metabolism in the lung with the application of new technologies. The latest single-cell sequencing and single-cell metabolomic technologies can be used to quantitatively evaluate the metabolism in individual cells. Autophagy reporter can be introduced to track dynamic change of autophagy in lung stem/progenitor cells at steady state or lung diseases. Combined genomics, proteomics, and metabolomics analyses may provide a systematic insight into mechanisms of pathophysiological characteristics of clinical respiratory diseases.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

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