Review Article

mTOR and autophagy in acute lung injury pathogenesis and therapeutic potential

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Abstract: Acute lung injury (ALI) poses a significant clinical challenge due to its high morbidity and mortality rates. Current treatment options are limited in their efficacy, necessitating the exploration of novel therapeutic targets. The mammalian target of rapamycin (mTOR), a crucial regulator of various cellular processes, has been implicated in the pathogenesis of ALI. Autophagy, a tightly regulated cellular degradation process controlled by mTOR, plays a pivotal role in the pathogenesis of ALI and cellular homeostasis. Mounting evidence also suggests that the mTOR pathway and autophagy play crucial roles in the pathogenesis and regulation of ALI. Herein, we reviewed the current understanding of how mTOR signaling and autophagy intersect in the context of ALI, with a focus on their roles across different cell types. This analysis highlights their dual roles in either promoting pulmonary injury or providing protection, depending on the specific cell types and different ALI models. Insights into the intricate balance between mTOR-mediated pathways and autophagic responses provide a foundation for developing targeted therapeutic strategies aimed at alleviating ALI through the modulation of these pathways. This review underscores the therapeutic potential of targeting mTOR and autophagy, presenting innovative and promising approaches for improving the clinical management and outcomes of ALI.

Keywords: Acute lung injury (ALI); mammalian target of rapamycin (mTOR); autophagy; pathogenesis; therapeutic potential

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Introduction

Acute lung injury (ALI) and its severe form, acute respiratory distress syndrome (ARDS), are highly prevalent and potentially life-threatening pathological conditions that are characterized by the rapid onset of inflammation and damage to the alveolar epithelium and pulmonary endothelium. The high incidence rates of ALI and ARDS contribute to a significant proportion of mortalities. This increased mortality rate is primarily attributed to sepsis and the consequent development of multiple organ failure (1,2). In 2016, the diagnostic criteria for ALI were observed in 10% of patients admitted to

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intensive care units (ICUs); furthermore, 23% of patients receiving mechanical ventilation were diagnosed with ALI (1). Unfortunately, disturbingly high mortality rates of up to 31% were observed even among individuals who had prompt resolution of ALI (3,4). Common clinical manifestations of ALI include a sudden onset of dyspnea, severe hypoxemia, and bilateral pulmonary edema, characterized by the accumulation of fluid in the pulmonary airspaces. Pneumonia, non-pulmonary sepsis, and aspiration are frequently identified as triggers for ALI (1,4). It is noteworthy that the coronavirus disease 2019 (COVID-19) pandemic contributed significantly to a surge in ALI cases, especially in individuals with severe viral pneumonia that progressed to acute respiratory distress syndrome (1,4). Other emerging causes, such as the use of e-cigarettes or vaping products, have also been recognized (5).

ALI is characterized by substantial impairment of both the vascular endothelium and alveolar epithelium, resulting in compromised lung function and dysregulated pulmonary inflammation (4). Current clinical interventions for ALI mainly focus on mechanical ventilation and symptomatic management, owing to a lack of consistently effective pharmacological interventions (4). Therefore, further investigation into the underlying pathophysiological mechanisms is warranted to facilitate the development of novel therapeutic strategies.

The mammalian target of rapamycin (mTOR) is a critical protein involved in several important signaling pathways. It is specifically targeted by rapamycin, which is known for its immunosuppressive, antitumor, and neuroprotective properties (6). mTOR plays a crucial role in the regulation of autophagy, a cellular degradation process that is vital for maintaining cellular homeostasis (7). Autophagy is closely related to various pulmonary diseases, including ALI. Despite advances in understanding mTOR signaling, autophagy, and their roles in ALI, several critical gaps remain in the literature. Additionally, the precise molecular mechanisms through which mTOR modulates autophagy in ALI have not yet been fully elucidated. This review aims to provide a comprehensive understanding of the regulatory function of mTOR in autophagy and its intricate contribution to the progression of ALI, paving the way for novel therapeutic strategies.

The primary database utilized for this review was PubMed; it was selected because of its comprehensive coverage of biomedical literature and relevance to this topic. The key search terms were “mTOR”, “autophagy”, and “acute lung injury”. These terms were used individually and in combination to ensure a thorough exploration of the literature. Experimental studies, clinical trials, and review articles that focused on the role of mTOR and/or autophagy in the context of ALI and provided mechanistic insights or therapeutic implications were included. Studies that were not directly related to mTOR, autophagy, or ALI were excluded. A total of 59 studies were reviewed after applying the inclusion and exclusion criteria.

mTOR and its regulation of autophagy

mTOR, a member of the phosphoinositide 3-kinase (PI3K)-related protein kinase subfamily, is composed of two distinct complexes: mechanistic target of rapamycin complex 1 (mTORC1) and mTORC2 (8). mTORC1 consists of five subunits: mTOR, regulatory protein associated with mTOR (RAPTOR), mammalian lethal with Sec13 protein 8/G protein β-subunit-like protein (mLST8/GβL), proline-rich AKT substrate of 40 kDa (PRAS40), and DEPTOR [dishevelled, egl-10, and pleckstrin (DEP) domain-containing mTOR-interacting protein]. Conversely, mTORC2 comprises mTOR, DEPTOR, mLST8, rapamycin-insensitive companion of mTOR (RICTOR), mitogen-activated protein kinase-associated protein 1 (mSin1), and protein observed with rictor-1 and 2 (PROTOR1/2) (8).

mTOR is responsive to numerous environmental cues, including low energy conditions or growth factor signals, and regulates cellular growth, metabolism, and survival through downstream signaling pathways (6). The tuberous sclerosis complex 1/2 (TSC1/2) is the central upstream regulator of mTORC1. The complex functions as a guanosine triphosphatase (GTPase)-activating protein (GAP) for the small GTPase, Ras homolog enriched in brain (Rheb). Inhibition of the TSC complex allows Rheb to remain in its active GTP-bound state, which directly activates mTORC1 (8).

The binding of growth factors, such as insulin, to their receptors leads to the activation of PI3K, which generates phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 activates protein kinase B (AKT), which in turn phosphorylates and inhibits TSC1/2, then activates Rheb, which stimulates mTORC1 (8). Similar to the PI3K/AKT pathway, growth factors could activate the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, also known as the Ras-Raf-MEK-ERK pathway. This pathway can lead to the activation of ERK. ERK can phosphorylate TSC2 at different sites than

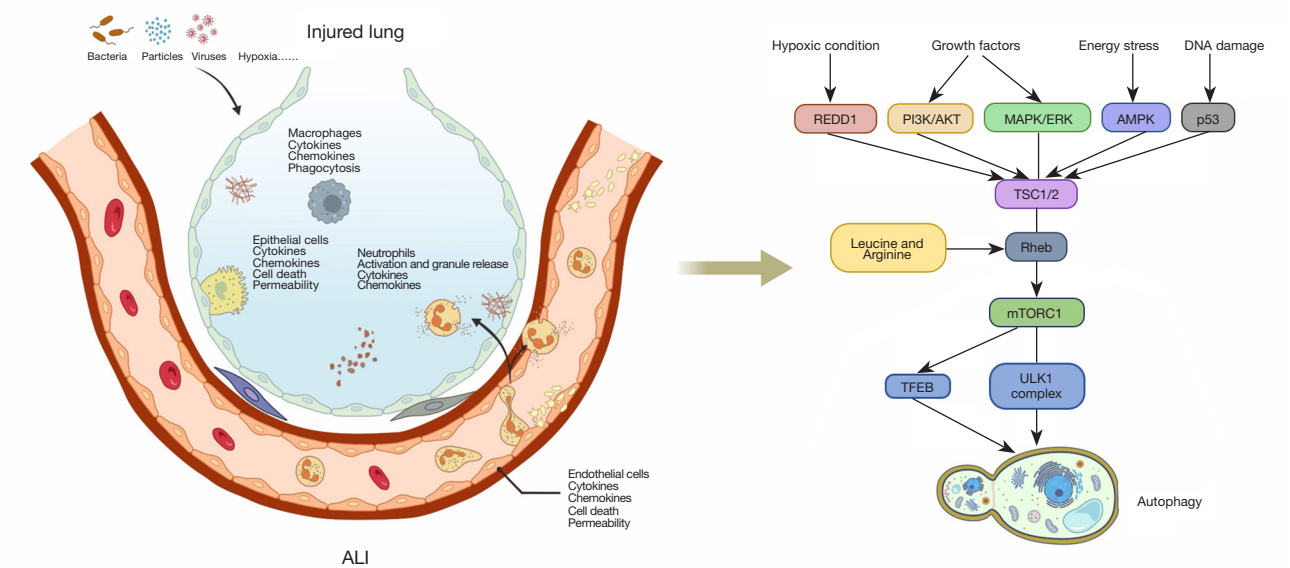

Figure 1 Schemata about the roles of mTOR and autophagy in ALI. Key upstream signals regulate autophagy through mTORC1 in the context of ALI. On the left, alveolar damage, immune cell infiltration, and increased permeability demonstrate how bacteria, viruses, or hypoxia trigger inflammation and further tissue damage. On the right, signals such as REDD1, PI3K/AKT, MAPK/ERK, AMPK, and p53 influence TSC1/2 and Rheb to control mTORC1 activity. When mTORC1 is active, autophagy is inhibited by preventing the activation of ULK1 complex and TFEB. AKT, protein kinase B; ALI, acute lung injury; AMPK, adenosine 5'-monophosphate-activated protein kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphoinositide 3-kinase; REDD1, regulated in development and DNA damage responses 1; Rheb, Ras homolog enriched in brain; TFEB, transcription factor EB; TSC1/2, tuberous sclerosis complex 1/2; ULK1, uncoordinated-51-like protein kinase.

AKT, which can also inhibit the TSC1/2 complex, thereby promoting mTORC1 activation (8). Moreover, amino acids, especially leucine and arginine, activate mTORC1 through the Rag GTPases, and recruit mTORC1 to the lysosomal surface, where it interacts with Rheb (8).

In instances of energy stress, the serine/threonine kinase LKB1 activates the adenosine 5'-monophosphate-activated protein kinase (AMPK) in response to low energy levels. AMPK phosphorylates and activates TSC2, enhancing its ability to inhibit mTORC1 (8). Under hypoxic conditions, regulated in development and DNA damage responses 1 (REDD1) is upregulated. REDD1 activates the TSC1/2 complex, leading to the inhibition of mTORC1 to conserve resources under low oxygen conditions (8). Under DNA damage and other cellular stress, p53 becomes activated, leading to expression of TSC2, thus, negatively regulating mTORC1 (8).

mTOR is a well-known negative regulator of autophagy (*Figure 1*). The activation of the uncoordinated-51-like protein kinase (ULK1) is an early step in autophagy, forming a complex with autophagy-related gene (ATG)13, ATG101, and focal adhesion kinase family-interacting protein (FIP200). mTORC1 phosphorylates ULK1, thereby blocking the initiation of autophagosome formation and negatively regulating the process of autophagy (8,9). Additionally, mTORC1 phosphorylates and inhibits the transcription factor EB (TFEB) family members, which are essential for the expression of several autophagy-related proteins and lysosomal factors (8,10). Similar to mTORC1, mTORC2 has also been shown to act as a negative regulator of autophagy. Several key molecular players involved in autophagy-related pathways have been directly associated with the activity of mTORC2 (11).

Role of autophagy in ALI

Autophagy is a highly conserved cellular degradation and recycling process that can be morphologically classified into three types: macroautophagy, microautophagy, and chaperone-mediated autophagy (12). All three types involve

the proteolytic degradation of cytosolic components at the lysosome through the action of lysosomal acid proteases. Serving as a cellular housekeeping process, autophagy not only eliminates protein aggregates, damaged organelles, and intracellular pathogens but also recycles the degradation products for reuse within cells. Dysregulation of autophagy has also been implicated in non-apoptotic cell death processes (13).

A growing body of evidence indicates that autophagy plays a vital role in maintaining cellular homeostasis and is involved in the pathogenesis of various diseases, particularly neurodegenerative conditions, inflammatory disorders, and cancer. Autophagic processes are controlled by a set of ATGs that are essential for the proper formation of autophagosomes (14). Notably, Beclin-1/ATG6 was the first mammalian autophagy-related gene identified and is known to play a significant role in the formation of the autophagosome as well as the maturation of autophagosomes and endosomes (15). Another critical protein in autophagy is microtubule-associated protein 1 light chain 3 (LC3), particularly its isoform LC3B, an autophagosomal ortholog of yeast ATG8. LC3B is lipidated with phosphatidylethanolamine, forming LC3-II, which serves as a reliable marker for autophagosomes in mammalian cells (16,17). These two proteins are commonly used as markers in autophagy research.

Autophagy has been observed to have both protective and detrimental effects on the pathogenesis and progression of ALI (18-20). On the one hand, autophagy can limit excessive inflammatory responses by degrading pro-inflammatory mediators and damaged mitochondria. By removing damaged organelles and proteins, autophagy promotes the survival and function of cells. On the other hand, overactive autophagy leads to excessive degradation of cellular components, contributing to cell death and worsening lung injury. The study has reported different levels of autophagy in different stages of lipopolysaccharide (LPS)-induced ALI, suggesting its involvement in the disease (21).

mTOR and autophagy in ALI

mTOR and autophagy are key regulators of the pathogenesis and resolution of ALI (*Figure 1*). Excessive mTOR activity can exacerbate inflammation and tissue damage, while insufficient mTOR activity can impair cell survival and tissue repair. Meanwhile, proper regulation of autophagy is essential for mitigating lung injury and promoting recovery. Their interplay determines the balance between inflammation, cell survival, and tissue repair, making them critical targets for therapeutic intervention. The roles of mTOR and autophagy have been found to vary among different cell types and different models. Several animal models of ALI have been utilized, and were induced by stimuli such as LPS, ischemia/reperfusion (I/R) injury, and cecal ligation and puncture (CLP).

Figure 1 shows how ALI develops and the upstream signals that control autophagy through mTORC1. On the left, alveolar and vascular structures face damage from pathogens or hypoxia. Injured epithelial and endothelial cells release cytokines, drawing immune cells into the lung. These cells produce more mediators, raising permeability and cell death. On the right, pathways such as PI3K/AKT, MAPK/ERK, AMPK, and p53 act on TSC1/2 and Rheb to regulate mTORC1. When active, mTORC1 inhibits ULK1 complex and TFEB, blocking autophagy. Under stress or limited nutrients, mTORC1 activity drops, allowing autophagy to proceed. Amino acids (e.g., leucine, arginine) also modulate mTORC1 through Rag GTPases, positioning it at the lysosome where Rheb refines autophagy control. In this context, we will discuss the specific roles of autophagy in various cell types, with an emphasis on the involvement of the mTOR pathway.

Epithelial cells

The intact alveolar epithelium functions as a robust defense against alveolar flooding. Disruption of epithelial cells, such as apoptosis or necrosis, as well as disruption of intercellular junctions, can impair fluid transport and increase epithelial barrier permeability (4).

Autophagy has been implicated in the pathogenesis of ALI, particularly in lung epithelial cells. However, as summarized in *Table 1*, the specific impact of autophagy varies across different models. In nanoparticle-induced ALI, deregulation of the AKT-TSC2-mTOR signaling pathway triggers autophagic cell death. Inhibition of autophagy with 3-methyladenine (3-MA) has been shown to reduce epithelial cell death and ameliorate ALI (22). Similarly, in hemagglutinin type 5 and neuraminidase type 1 (H5N1) influenza virus infection, autophagic cell death in lung epithelial cells is driven by mTOR suppression or AKT-TSC pathway activation. Blocking autophagy via Beclin-1 knockdown or 3-MA reduces epithelial cell loss and improves outcomes (23,24).

Additional investigations further reinforce the notion

Table 1 Summary of major studies of mTOR and autophagy in epithelial cells in models of lung injury

Role of autophagy in ALI	Lung injury model(s)	Majoy outcome(s) related to autophagy and mTOR	References
Autophagy as a detrimental mechanism	Nanoparticle	Autophagic cell death was triggered by deregulating the AKT-TSC2-mTOR signaling pathway	Li *et al.*, 2009 (22)
	H5N1	H5N1 caused autophagic cell death through suppression of mTOR signaling. Inhibition of autophagy significantly reduced H5N1 mediated cell death	Ma *et al.*, 2011 (23)
	H5N1	H5N1 induced autophagic cell death through a pathway involving AKT-TSC and mTOR. Blocking autophagy increased the survival rate of mice and ameliorated the ALI and mortality caused by H5N1 infection	Sun *et al.*, 2012 (24)
	Ventilator	H2S treatment alleviated lung injury by reducing autophagy and ER stress in rats	Ge *et al.*, 2019 (25)
	LPS	Autophagy inhibition through PI3K/AKT/mTOR pathway was involved in H2S prevention of LPS-induced ALI in mice	Xu *et al.*, 2018 (26)
	I/R	Xenogeneic and allogeneic mesenchymal stem cells protected the lung against I/R injury by suppressing the inflammatory, oxidative stress, and autophagic signaling	Lin *et al.*, 2020 (27)
	LPS	MicroRNA-34a may attenuate ALI damage by targeting FoxO3 to inhibit excessive autophagic activity in AECII	Song *et al.*, 2017 (28)
	Hyperoxia	Hyperoxia causes lung injury via mTOR-mediated AECII autophagy	Ren *et al.*, 2024 (29)
	LPS	Liensinine alleviates LPS-induced ALI by reducing autophagy through PI3K/AKT/mTOR signaling pathway	Wang *et al.*, 2023 (30)
	LPS	Expression of advanced glycation end-product receptor was promoted by LPS, and it associated with activation of autophagy and cytokine levels. Treatment with 3-MA protected lungs from damage	Xiong *et al.*, 2023 (31)
Autophagy as a protective mechanism	CLP	Rapamycin treatment activated autophagy, limited the CLP-induced proinflammatory response, and downregulated apoptotic activity	Yen *et al.*, 2013 (32)
	LPS	LPS activated mTOR and decreased autophagy thus promoted ALI. Treatment of rapamycin could suppress the mTOR activity and notably ameliorate ALI	Hu *et al.*, 2016 (33)
	Hyperoxia	Inhibiting regulatory-associated protein of mTOR in hyperoxia settings limited lung injury by increased autophagy, decreased apoptosis, improved lung architecture, and increased survival	Sureshbabu *et al.*, 2016 (34)
	LPS	Cinobufagin enhanced autophagy through the p53/mTOR pathway in LPS-induced ALI thus alleviated lung injury	Wang *et al.*, 2022 (35)
	LPS	ER stress-mediated autophagy has cytoprotective effects on LPS-induced lung injury through AKT/mTOR signaling pathway, and 3-MA exacerbates cytotoxicity induced by LPS	Zeng *et al.*, 2017 (36)
	LPS	Autophagy is induced by targeting mTOR thus ameliorates LPS-induced ALI	Wei *et al.*, 2020 (37)
	LPS	Isorhamnetin alleviates LPS-induced ALI by inhibiting mTOR signaling and activating autophagy	Yang *et al.*, 2022 (38)
	LPS	Ketamine treatment activates AMPK thus inhibiting the mTOR pathway and promoting autophagy, thereby alleviating the apoptosis of AECII cells	Cao *et al.*, 2022 (39)
	Hyperoxia	Autophagosome formation is increased after hyperoxia, and silencing LC3B promotes hyperoxia-induced cell death in epithelial cells, whereas overexpression of LC3B provides cytoprotection	Tanaka *et al.*, 2012 (40)
	LPS	WWOX activates autophagy in lung epithelial cells and protect against LPS-induced ALI, which is partly related to the mTOR signaling pathway	Wang *et al.*, 2023 (41)

3-MA, 3-methyladenine; AECII, alveolar type II epithelial cells; AKT, protein kinase B; ALI, acute lung injury; AMPK, adenosine 5'-monophosphate-activated protein kinase; CLP, cecal ligation and puncture; ER, endoplasmic reticulum; FoxO3, Forkhead box O3; H2S, hydrogen sulfide; H5N1, hemagglutinin type 5 and neuraminidase type 1; I/R, ischemia/reperfusion; LC3B, microtubule-associated protein 1 light chain 3B; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; TSC, tuberous sclerosis complex.

that autophagy inhibition can be protective. For instance, hydrogen sulfide (H2S) ameliorates lung damage by mitigating autophagy (25,26), through the PI3K/AKT/mTOR pathway (26). Xenogeneic and allogeneic mesenchymal stem cells could protect the lung against I/R injury, partly through the downregulation of autophagy in rats (27). MicroRNA-34a suppresses excessive autophagic activity in alveolar type II epithelial cells (AECII) to reduce cellular damage in LPS-induced ALI (28). Hyperoxia has been shown to induce lung injury by enhancing AECII autophagy via activation of the mTOR pathway (29). Liensinine was reported to alleviate LPS-induced ALI by blocking autophagic flux via PI3K/AKT/mTOR signaling pathway (30). Furthermore, advanced glycation end-product receptor inhibition alleviated LPS-induced lung injury by directly suppressing autophagic apoptosis of alveolar epithelial cells (31).

Conversely, other studies indicate that autophagy activation may be beneficial. Rapamycin, the mTOR inhibitor, has been shown to activate autophagy, limit the proinflammatory response, and downregulate apoptotic activity in CLP-induced ALI (32). Whereas, in LPS-induced ALI, the activation of mTOR suppresses autophagy, thereby contributing to inflammatory responses in the epithelium, while rapamycin effectively alleviates lung injury (33). Upon exposure to hyperoxia, activating autophagy through the inhibition of the regulatory-associated protein of mTOR demonstrates a protective role with an antiapoptotic response (34). Additionally, cinobufagin, a primary component isolated from cinobufotalin, was proven to enhance autophagy through the p53/mTOR pathway in LPS-induced ALI (35). Other studies have demonstrated that targeting mTOR to induce autophagy could ameliorate LPS-induced ALI (36-39).

In line with this protective role, silencing LC3B augments hyperoxia-induced cell death in epithelial cells, whereas LC3B overexpression confers protection (40). The gene *WWOX*, linked to lung diseases, helps reduce LPS-induced lung injury by activating autophagy through mTOR (41). Overall, these studies provide valuable insights into the intricate association between autophagy and lung epithelial cells in the pathogenesis of ALI. Modulating autophagy by targeting the mTOR pathway holds significant promise as a potential therapeutic approach for ALI. However, further comprehensive investigations are necessary to fully elucidate the intricate molecular mechanisms underlying this relationship.

Endothelial cells

The pulmonary vascular endothelium serves a dual role as both a physical barrier and an active regulator of various physiological processes, including vessel permeability, signaling, and angiogenesis (42). Disruption of the vascular endothelial cells can lead to an increase in capillary permeability, contributing significantly to the development of ALI (42).

Table 2 primarily summarizes the literature on the role of autophagy in endothelial cells during ALI. Some reports show that blocking or reducing autophagy can protect the endothelium. One study found that 3-MA lowers lung leakage and swelling, which helps repair the endothelial barrier (43). Astragaloside IV also decreases autophagy, raises cell survival, strengthens tight junctions, and reduces cell death (44). In another study, blocking autophagy by using 3-MA or ATG5 small interfering RNA (siRNA) cut endothelial permeability (45). Autophagy has been extensively studied in the context of endothelial cell inflammation and vascular permeability. Silencing the Beclin1 gene has been shown to restore endothelial cell barrier integrity (46). In hemorrhagic shock-induced ALI, autophagy was increased in lung tissue and contributed to lung problems (47). Similarly, research also indicates that autophagy mediates I/R injury in endothelial cells (48).

Other studies show that raising autophagy can be beneficial. Hydrogen-rich saline, for example, triggered autophagy in LPS-induced ALI and downregulated the mTOR/TFEB pathway, which reduced lung injury and endothelial dysfunction (49). Additional reports noted that stopping autophagy made LPS-induced ALI worse (50,51). Apelin-13 lowers lung damage and vascular leakage by increasing autophagic flux (52). Small extracellular vesicles derived from adipose-derived stem cells effectively alleviated LPS-induced endothelial cell barrier damage and lung injury, while autophagy inhibition markedly weakened the therapeutic effect (53). Hyperoside also reduces endothelial damage through ATG13-mediated autophagy, though stopping this pathway cancels its protective role (54). Transplantation of mesenchymal stem cells was proven to significantly reduce the severity of LPS-induced ALI in mice by increasing autophagy in endothelial cells to promote their survival (55). Additionally, sevoflurane has been shown to suppress apoptosis and inflammation by activating protective autophagy (56). Adipose-derived stem cells significantly alleviated LPS-induced microvascular

Table 2 Summary of major studies of mTOR and autophagy in endothelial cells in models of lung injury

Role of autophagy in ALI	Lung injury model(s)	Majoy outcome(s) related to autophagy and mTOR	References
Autophagy as a detrimental mechanism	LPS	3-MA reduced lung vascular leakage and tissue edema, and it was also effective in reducing the levels of proinflammatory mediators and lung neutrophil sequestration induced by LPS	Slavin *et al.*, 2018 (43)
	LPS	Astragaloside IV might suppress autophagy initiation directly or indirectly through suppressing the oxidative stress and inflammatory response, which further enhances the cell viability and tight junction and reduces apoptosis in LPS-stimulated pulmonary endothelial ARDS cell model	Liu *et al.*, 2020 (44)
	LPS	Increased endothelial permeability can be significantly alleviated by autophagy inhibitor 3-MA and ATG5 siRNA	Zhao *et al.*, 2022 (45)
	Thrombin and LPS	Inhibition of autophagic activity could restore endothelial cells barrier integrity	Leonard *et al.*, 2019 (46)
	Hemorrhagic shock	The autophagy levels were enhanced in pulmonary tissue leading a pulmonary dysfunction, 17β-estradiol treatment attenuated the adverse changes after hemorrhagic shock, which was reversed by rapamycin administration	Sun *et al.*, 2023 (47)
	I/R	Autophagy was promoted to induce endothelial migration and apoptosis in I/R injury	Xie *et al.*, 2018 (48)
Autophagy as a protective mechanism	LPS	Hydrogen-rich saline inhibits LPS-induced ALI and endothelial dysfunction by regulating autophagy through mTOR/TFEB signaling pathway	Fu *et al.*, 2020 (49)
	LPS	Autophagy maintains the integrity of endothelial barrier. Inhibiting autophagy further exacerbated lung injury	Zhang *et al.*, 2018 (50)
	LPS	Autophagy activity is required for the maintenance of endothelial cell barrier integrity, and autophagy inhibition aggravated the formation of intercellular gaps	Dong *et al.*, 2018 (51)
	LPS	Apelin-13 ameliorates pulmonary vascular permeability in mice with ALI induced by LPS, which may be related to enhanced phosphorylation of AMPK to regulate mitochondrial function and autophagy	Kong *et al.*, 2021 (52)
	LPS	Small extracellular vesicles derived from adipose-derived stem cells protected against LPS-induced pulmonary microvascular barrier damage and acute lung injury, and autophagy is a positive mediator of this function	Li *et al.*, 2022 (53)
	LPS and CLP	Hyperoside treatment attenuated sepsis-induced ALI by regulating autophagy and inhibiting inflammation	Mai *et al.*, 2023 (54)
	LPS	Transplantation of mesenchymal stem cells may alleviate LPS-ALI through downregulation of miR-142a-5p, which allows pulmonary endothelial cells to increase Beclin-1-mediated cell autophagy	Zhou *et al.*, 2016 (55)
	LPS	Sevoflurane suppressed apoptosis and inflammation via activating protective autophagy through AMPK-ULK1 pathway, thereby restrained ALI	Fu *et al.*, 2022 (56)
	LPS	Adipose-derived stem cells paracrine effects play a protective role in LPS-induced pulmonary microvascular barrier injury, and autophagy is a positive mediating factor in this process	Li *et al.*, 2019 (57)
	LPS and CLP	Overexpression of estrogen-related receptor alpha promoted the formation of autophagic flux and ameliorated sepsis-induced ALI	Xia *et al.*, 2023 (58)
	CLP	Plasma extracellular vesicle carrying microRNA-210-3p inhibit autophagy and activate inflammation. Improvements in vascular density and autophagosome formation were detected in adenovirus-anti-miR-210-3p treated mice after CLP injury	Li *et al.*, 2021 (59)
	I/R	Integrin αvβ5 inhibition protected against I/R-induced lung injury by promoting endothelial cells autophagy, thus alleviating cell permeability, decreasing the apoptosis ratio and activating caspase-3 expression	Zhang *et al.*, 2017 (60)
	I/R	Autophagy plays a protective role in I/R-induced lung injury by ameliorating conjunction damage and cell death	Zhang *et al.*, 2015 (61)

3-MA, 3-methyladenine; ALI, acute lung injury; AMPK, adenosine 5'-monophosphate-activated protein kinase; ATG, autophagy-related gene; CLP, cecal ligation and puncture; I/R, ischemia/reperfusion; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; siRNA, small interfering RNA; TFEB, transcription factor EB; ULK1, uncoordinated-51-like protein kinase.

barrier injury, and inhibiting autophagy weakened paracrine functions and protective effects (57). Additionally, estrogen-related receptor alpha was demonstrated to protect against sepsis-induced ALI through the regulation of the balance between autophagy and apoptosis; the promotion of its expression enhanced autophagy and reduced CLP-induced ALI (58). Plasma extracellular vesicles carrying microRNA-210-3p block autophagy through ATG7, which increases inflammation in CLP-induced ALI (59). Integrin αvβ5 inhibition was found to protect against I/R-induced lung injury by promoting autophagy, thus alleviating cell permeability and decreasing the apoptosis ratio (60). In another research, autophagy has also been shown to have a protective effect as it attenuates endothelial cell damage and mitigates cell death (61).

Overall, the impact of autophagy on endothelial cells in ALI is not straightforward. Some studies show that reducing autophagy helps maintain barrier function, while others indicate that promoting autophagy is crucial for cell survival and repair. These findings point to a complicated balance: autophagy can both protect and damage the endothelium under different conditions. More work is needed to understand how best to regulate autophagy to treat ALI.

Macrophages

Macrophages play a crucial role in initiating and maintaining the pulmonary immune response and homeostasis (62). Macrophages are recruited to the lungs in the presence of infection or injury, and this can exacerbate the inflammatory process (62). Macrophage autophagy primarily reduces pulmonary inflammation and lung injury, although it can worsen lung injury in some animal models (62).

Table 3 provides a comprehensive overview of studies investigating the impact of autophagy on macrophages in ALI. Many studies link increased macrophage autophagy with better outcomes in ALI. One report found that GYY4137, a novel H2S donor, blocks mTOR signaling, raises autophagy, and lessens lung injury (63). Another showed that glycyrrhizic acid lowers LPS-induced injury through the PI3K/AKT/mTOR pathway, and 3-MA can reverse this benefit (64). A separate investigation indicates that a cobalquinone B derivative triggers autophagy in alveolar macrophages by blocking AKT-mTOR, improving bacterial clearance and limiting lung damage in a *Pseudomonas aeruginosa* model (65). In acute radiation pneumonitis, hydrogen-rich saline stops polarization and reduces oxidative stress, then activates autophagy via AMPK/mTOR/ULK1 (66). Meanwhile, irisin repairs autophagy flux through AMPK/mTOR, lowering particulate matter 2.5 (PM2.5)-induced lung injury (67). Moreover, BML-111 (a lipoxin A4 receptor agonist) (68) and early-stage autophagy activation (69) both lower alveolar macrophage apoptosis. Strengthening autophagy can additionally suppress the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, thereby limiting interleukin (IL)-1β and IL-18 release (70-73).

Despite these benefits, other studies show that macrophage autophagy can contribute to lung damage. Complement C5a promotes alveolar macrophage apoptosis through an autophagy-related pathway, disrupting pulmonary homeostasis (74). Another study indicates that macrophage autophagy boosts inflammation (75). In LPS-induced models, resveratrol (a strong SIRT-1 activator) reduces cell death by blocking autophagy, though rapamycin nullifies this benefit (76). Hydrogen-rich saline also shields the lungs during sepsis by lowering autophagy, adjusting macrophage polarization, and reducing apoptosis (77).

Taken together, these findings highlight the dual role of macrophage autophagy in ALI. In many scenarios, activating autophagy in macrophages limits inflammation and promotes tissue repair. Yet, under different conditions, heightened autophagy can worsen lung damage by increasing apoptosis and inflammation. Recognizing these context-dependent outcomes is essential for developing effective treatments that target macrophage autophagy in ALI.

Neutrophils

The accumulation of white blood cells, particularly neutrophils, in the lung and alveolar space is clinically and pathologically significant in ALI (4). This process involves the migration of activated neutrophils into the lung to combat inflammation and infection. However, excessive accumulation of neutrophils can lead to tissue damage and worsen lung injury.

Researches about the impact of autophagy on neutrophils in ALI are shown in *Table 4*. Several reports indicate that promoting autophagy in neutrophils reduces their damaging effects. In models with impaired autophagic flux, higher neutrophil extracellular traps (NETs) formation heightens inflammation (78). NETs are web-like structures that are released by activated neutrophils to trap and kill pathogens. By contrast, interventions that restore autophagy lower NET release and help contain the inflammatory response. Rapamycin also lowers polymorphonuclear neutrophil

Table 3 Summary of major studies of mTOR and autophagy in macrophage in models of lung injury

Role of autophagy in ALI	Lung injury model(s)	Majoy outcome(s) related to autophagy and mTOR	References
Autophagy as a protective mechanism	LPS	H2S could improve autophagy and attenuate lung injury in sepsis-induced ALI by blocking mTOR signaling	Li *et al.*, 2022 (63)
	LPS	Glycyrrhizic acid inhibits the production of inflammatory factors in LPS-induced ALI by regulating the PI3K/AKT/mTOR pathway related autophagy, which can be reversed by 3-MA	Qu *et al.*, 2019 (64)
	Pseudomonas aeruginosa	Cobalquinone B derivative blocks the AKT-mTOR signaling pathway to induce autophagy in mice alveolar macrophages, thereby enhancing bacterial clearance and attenuating lung injury	Zhu *et al.*, 2020 (65)
	Radiation	Hydrogen-rich solution inhibits M1 polarization and alleviated oxidative stress to activate autophagy by regulating the AMPK/mTOR/ULK1 signaling pathway	Yin *et al.*, 2024 (66)
	PM2.5	Irisin performs protective effects by activating autophagy through AMPK/mTOR signaling pathway	Ma *et al.*, 2023 (67)
	LPS	Lipoxin A4 receptor agonist BML-111 stimulated autophagy in alveolar macrophages, attenuated the LPS-induced cell apoptosis and promotes the resolution of ALI by targeting the MAPK signaling but not mTOR pathway	Liu *et al.*, 2018 (68)
	I/R	Rapamycin decreases the unfolded protein response and increases superoxide dismutase activities and decreased malondialdehyde levels, whereas 3-MA had the opposite effect	Fan *et al.*, 2016 (69)
	LPS	Rapamycin protects mice against LPS-induced ALI partly by inhibiting the production and secretion of IL-1β and IL-18	Jia *et al.*, 2019 (70)
	MTDs	Autophagy alleviates alveolar macrophage inflammatory response and ameliorates ALI by inhibiting NLRP3 inflammasome activation, whereas 3-MA negatively and rapamycin positively affected this process	Peng *et al.*, 2021 (71)
	LPS and CLP	Geranylgeranyl diphosphate synthase 1 regulated NLRP3 inflammasome activation via autophagy. Treatment of 3-MA enhanced the lung injury in CLP-induced septic mice	Li *et al.*, 2021 (72)
	Klebsiella pneumoniae	Chrysophanol ameliorates ALI through inhibiting pro-inflammatory cytokines partly by strengthening autophagy	Jiang *et al.*, 2023 (73)
Autophagy as a detrimental mechanism	Intestinal I/R	Complement C5a produced during lung injury binds to C5a receptor in alveolar macrophages, initiates downstream signaling that promotes autophagy, leading to apoptosis of alveolar macrophages	Hu *et al.*, 2014 (74)
	I/R	Macrophage autophagy facilitates the inflammation response in lungs undergoing I/R injury	Liu *et al.*, 2017 (75)
	LPS	Resveratrol administration reduces LPS-induced cell apoptosis by altering the unbalance of Bax/Bcl-2 and inhibiting LPS-induced autophagy	Yang *et al.*, 2018 (76)
	LPS	LPS treatment leads to an increase in autophagy, apoptosis, and M1 polarization but a decrease in M2 polarization. These effects are reversed by administration of hydrogen-rich saline. 3-MA parallelled the effects of hydrogen-rich saline	Qiu *et al.*, 2021 (77)

3-MA, 3-methyladenine; AECII, alveolar type II epithelial cells; AKT, protein kinase B; ALI, acute lung injury; AMPK, adenosine 5'-monophosphate-activated protein kinase; CLP, cecal ligation and puncture; ER, endoplasmic reticulum; FoxO3, Forkhead box O3; H2S, hydrogen sulfide; H5N1, hemagglutinin type 5 and neuraminidase type 1; I/R, ischemia/reperfusion; LC3B, microtubule-associated protein 1 light chain 3B; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; TSC, tuberous sclerosis complex.

Table 4 Summary of major studies of mTOR and autophagy in neutrophil in models of lung injury

Role of autophagy in ALI	Lung injury model(s)	Majoy outcome(s) related to autophagy and mTOR	References
Autophagy as a protective mechanism	Sepsis	The level of neutrophil extracellular traps was increased, which led to impairment of autophagic flux and deterioration of the disease. Rapamycin also alleviated lung injury	Qu *et al.*, 2022 (78)
	CLP	Autophagy activation participated in the pathophysiologic process of sepsis, and alleviated the cytokine excessive release and lung injury in sepsis	Zhao *et al.*, 2019 (79)
	LPS	The level of NET release was reduced and autophagy is elevated by PD-L1 knockout in ARDS neutrophils both in vivo and in vitro. This effect could be reversed by inhibition of autophagy	Zhu *et al.*, 2022 (80)
	PAM or LPS	mTORC1 activation is essential in TLR2- and TLR4-induced neutrophil activation, as well as in the development and severity of acute lung injury	Lorne *et al.*, 2009 (81)
Autophagy as a detrimental mechanism	LPS	Autophagy was required for neutrophil activation and granule release. Ethyl pyruvate alleviated ALI through inhibition of autophagy-induced granule release by neutrophils	Zhu *et al.*, 2017 (82)

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CLP, cecal ligation and puncture; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; NET, neutrophil extracellular trap; PAM, Pam(3) Cys-Ser-(Lys)(4); PD-L1, programmed death ligand 1; TLR, Toll-like receptor.

counts and cytokine levels in CLP-induced ALI, hinting at a protective role for autophagy; conversely, inhibiting autophagy with 3-MA worsens these markers (79). Programmed death ligand 1 (PD-L1) also maintains the release of NETs by regulating autophagy via PI3K/AKT/mTOR pathway in ARDS (80). Meanwhile, mTORC1 drives neutrophil activation in response to Toll-like receptor (TLR)2/4 stimulation, and rapamycin-mediated mTORC1 inhibition lowers cytokine release and lung damage (81).

Another study shows that inhibition of autophagy in neutrophils reduces degranulation and alleviates LPS-induced ALI (82). Thus, although neutrophil accumulation is crucial for infection control, misregulated autophagy or mTORC1 activity can turn a protective immune response into one that harms lung tissue.

Generally, the dysregulation of neutrophil function, impairment of autophagy, and mTORC1 activation contribute to the development and worsening of ALI. Understanding the intricate interplay between neutrophil activation, autophagy, and mTORC1 signaling holds promise for the development of novel therapeutic strategies for ALI.

Discussion

Current studies suggest that autophagy plays a complex and context-dependent role in ALI, offering potential therapeutic targets. Balancing autophagy activation and inhibition, depending on the stage and severity of the lung injury, could improve the outcomes of patients with ALI. Targeting the mTOR pathway to modulate autophagy may enhance the clearance of damaged cellular components, reduce inflammation, and promote tissue repair, thereby ameliorating the severity of ALI. This therapeutic approach holds potential due to its ability to address the underlying cellular dysfunctions associated with ALI, offering a novel avenue for treatment.

It is worth noting that DEPTOR is a natural inhibitor of mTOR (83). The role of DEPTORs in inhibiting mTOR activity makes it an intriguing emerging target for the treatment of ALI. The specificity of DEPTOR in inhibiting mTOR, along with its natural presence in the body, suggests that therapies based on DEPTOR modulation could offer a more nuanced and potentially safer alternative to broad-spectrum mTOR inhibitors, such as rapamycin. Recent research has highlighted DEPTOR's potential in modulating the mTOR pathway to achieve therapeutic benefits in various diseases, including cancer and metabolic disorders. However, its role in ALI is still under investigation. By increasing DEPTOR levels or mimicking its inhibitory effects on mTOR, it may be possible to develop new therapeutic strategies that specifically target

the pathological processes underlying ALI. Further research is needed to fully understand the regulatory mechanisms of DEPTOR in lung tissues and its impact on the complex pathophysiology of ALI.

Although our review comprehensively examined the role of mTOR and autophagy in ALI, it has some limitations. This review's reliance on published literature may be subject to publication bias, favoring studies with positive results. Additionally, the heterogeneity of the studies reviewed, including differences in experimental models and methodologies, poses a challenge in drawing unified conclusions. Furthermore, the rapidly evolving nature of research in this field suggests that more recent studies may have been published since the literature search for this review was conducted, potentially affecting the relevance and applicability of the review's findings.

Conclusions

Future treatment strategies for the management of ALI could involve a combination of mTOR inhibitors and autophagy modulators, tailored to the patient's specific pathophysiological condition. Furthermore, understanding the precise molecular mechanisms governing mTOR and autophagy in ALI could lead to the development of more targeted therapies, minimizing potential side effects and maximizing therapeutic efficacy. The continued exploration of these pathways in ALI research holds significant potential for advancing treatment options and improving patient outcomes.

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Footnote

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