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mTOR signaling in airway epithelial homeostasis, aging, and diseases

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Abstract

Through the proliferation, differentiation, and survival of various stem and progenitor cells, the airway epithelium preserves homeostasis. To regulate these activities, mTOR signaling combines metabolic and environmental factors. The study reviews the role of mTOR signaling in airway epithelial homeostasis and its dysregulation in airway aging, emphysema, ARDS, and lung cancer. This review combines experimental and clinical data from lineage tracing, organoid systems, genetic mouse models, and patient-derived samples to identify the cell-specific roles of mTORC1 and mTORC2 signaling in airway epithelial stem/progenitor cell homeostasis, aging, and the pathology of disease. Balanced mTOR signaling is crucial for airway epithelial integrity by regulating basal stem cell proliferation, differentiation, and epithelial cell survival. Temporary activation of mTORC1 promotes proper differentiation during organoid formation, whereas persistent hyperactivation leads to stem cell exhaustion, cellular senescence, and impaired regeneration during aging. Aberrant mTOR activation contributes to alveolar degradation in emphysema, worsens inflammation and autophagy suppression in ARDS, and promotes carcinogenesis through PI3K/AKT/mTOR pathway dysregulation in lung cancer. Pharmacological manipulation of mTOR, particularly context-specific and dose-controlled inhibition, explains therapeutic potential but also contains risks of compromised tissue repair when used over an extended period of time. In conclusion, the mTOR signaling is a key modulator of aging, disease progression, and airway epithelial homeostasis. Its dual function emphasizes that accurate disease-specific stage adjustment is more important than widespread inhibition. Understanding cell-type-specific mTOR activities will allow future research on targeted therapeutic strategies to maintain epithelial healing and reduce bad outcomes.

Keywords airway epithelial homeostasis | mTOR signaling | dysregulation | aging | diseases

Introduction

The lung is a largely quiescent tissue with a regeneration turnover of approximately seven years, yet it possesses an extraordinary ability to heal after an injury. The primary function of lung tissue is to exchange gas, that is, to absorb oxygen and release carbon dioxide, and it acts as a physical barrier against different harmful compounds from the environment. It is readily and regularly broken by various stimuli, such as pathogens, cigarette smoke, and airborne pollutants, forcing it to quickly heal itself to maintain cell number, cell composition, and function (Hogan *et al.*, 2014; Zepp & Morrisey, 2019). This intense homeostasis is achieved by several multipotent stem cells or progenitor cells located along the airway and through various signaling pathways (Rock & Hogan, 2011; Gilpin et al., 2016; Wu *et al.*, 2022).

Several stem cells are located along the airway (**Figure 1**), such as basal cells residing within submucosal glands found in proximal airways, variant club stem cells positioned at neuroepithelial bodies (NEBs) found in bronchioles, bronchioalveolar stem cells (BASCs) located at the bronchioalveolar duct junctions (BADJs) found at the branch point of alveoli,

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and alveolar type 2 (AT2) stem cells residing within alveoli found at the tip of the airway (Giangreco *et al.*, 2007; Jones-Freeman & Starkey, 2020).

Among the various signaling pathways that regulate homeostasis in the airway, mammalian target of rapamycin (mTOR) signaling reportedly plays a crucial role in lung development and various diseases. Dysregulation of this signaling pathway is involved in diseases such as fibrosis, asthma, chronic obstructive pulmonary disease, bronchopulmonary dysplasia, pulmonary hypertension, and lymphangioleiomyomatosis (LAM) (Bao *et al.*, 2025). Dysregulation of this signaling pathway is also involved in aging and various illnesses, such as emphysema (Delgoffe *et al.*, 2009; Houssaini *et al.*, 2018; Kurimoto *et al.*, 2013), acute respiratory distress syndrome (ARDS), and lung cancer (Tan, 2020).

The airway epithelium acts as a barrier against pathogens and environmental insults while participating in mucociliary clearance (Hiemstra *et al.*, 2015). When the airway epithelium is injured, stem cells migrate to cover areas where differentiated epithelial cells are lacking. They then differentiate to form a healthy epithelial cell layer again (Hiemstra *et al.*, 2015).

The mechanistic target of rapamycin (mTOR) works through two separate complexes, mTORC1 and mTORC2, which are essential for many cellular homeostasis functions, including protein synthesis, metabolism, survival, autophagy, organelle biogenesis, and transcription (Lipton & Sahin, 2014). In this study, we briefly review the role of mTOR signaling in airway homeostasis, aging, and various illnesses, including emphysema, acute respiratory distress syndrome, and cancer. This review examines mTOR signaling in airway stem/progenitor cells that govern airway epithelial homeostasis, providing an epithelial cell-specific perspective beyond whole-lung analyses. In contrast, Bao *et al.* (2025) reviewed mTOR signaling across embryonic stages to analyze its role in whole-lung development. We further identified age-related epithelial changes and outlined a framework for identifying adult epithelial tissue-specific disorders and susceptibilities overlooked by Bao *et al.*

Overview of mTOR signaling with upstream target

mTOR, a serine/threonine kinase, belongs to the phosphatidylinositol 3-kinase (PI3K) family and plays a crucial role in regulating cell cycle progression, homeostasis, survival, aging, and protein and lipid metabolism (Lawrence & Nho, 2018). mTOR forms two complexes, mTORC1 and mTORC2, by interacting with numerous adaptor proteins (**Figure 2**) (Laplante & Sabatini, 2009). mTORC1 includes a proline-rich AKT substrate 40 kDa (PRAS40), mammalian lethal with Sec13 protein 8 (mLST8), DEP-domain-containing mTOR-interacting protein (Deptor), and regulatory-associated protein mTOR (Raptor). mTORC2 includes mLST8, Deptor, and the rapamycin-insensitive companion of mTOR (Rictor). Each complex contains distinct upstream regulators and downstream targets, leading to varied responses to rapamycin, an mTOR inhibitor (Laplante & Sabatini, 2009). mTORC1 is highly sensitive to rapamycin and governs cell growth and metabolism, whereas mTORC2 regulates cell proliferation and survival, but shows less sensitivity.

mTORC1 is influenced by various mechanisms, including growth hormones, cellular stress, low oxygen supply, DNA breakage, reactive oxygen species, nutrients such as glucose and amino acids, and proinflammatory cytokines such as tumor necrosis factor alpha (TNFα). Growth and mitogenic fac-

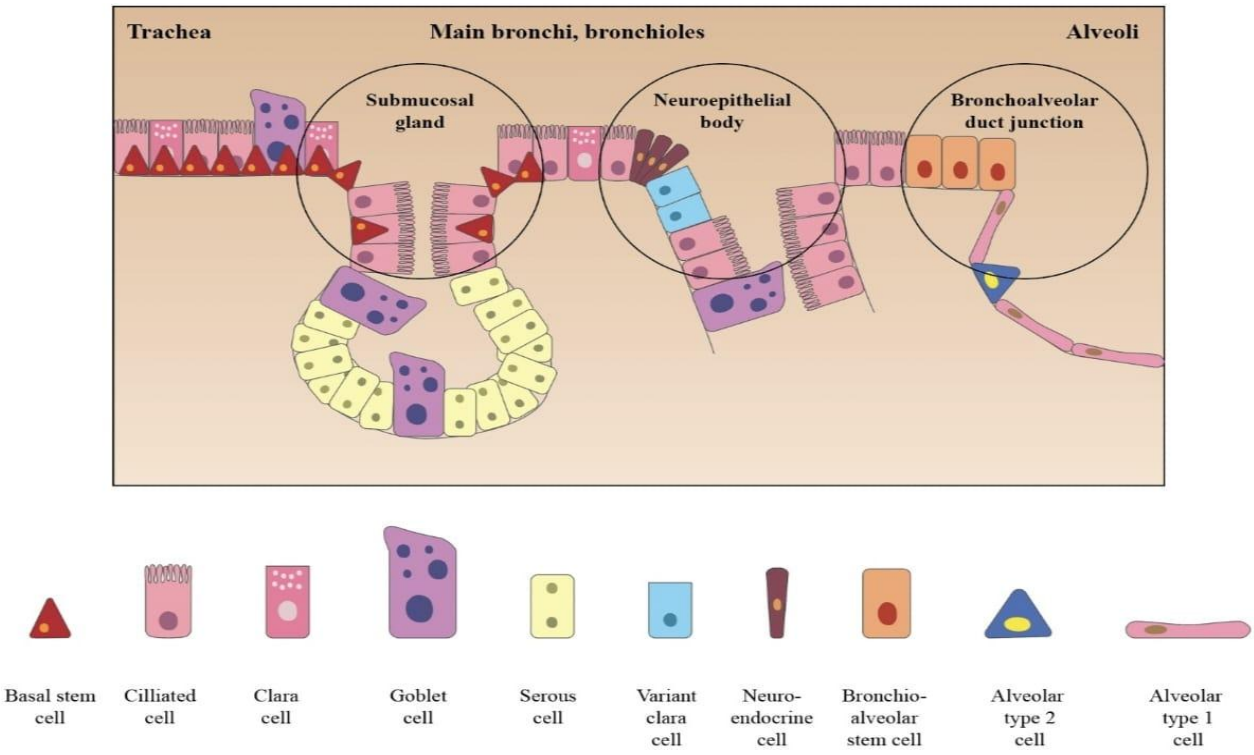

Figure 1 Schematic representation of the location of the various cell kinds that form the epithelial surfaces of the airways. The stem cell niches are highlighted within circles (Succony & Janes, 2014).

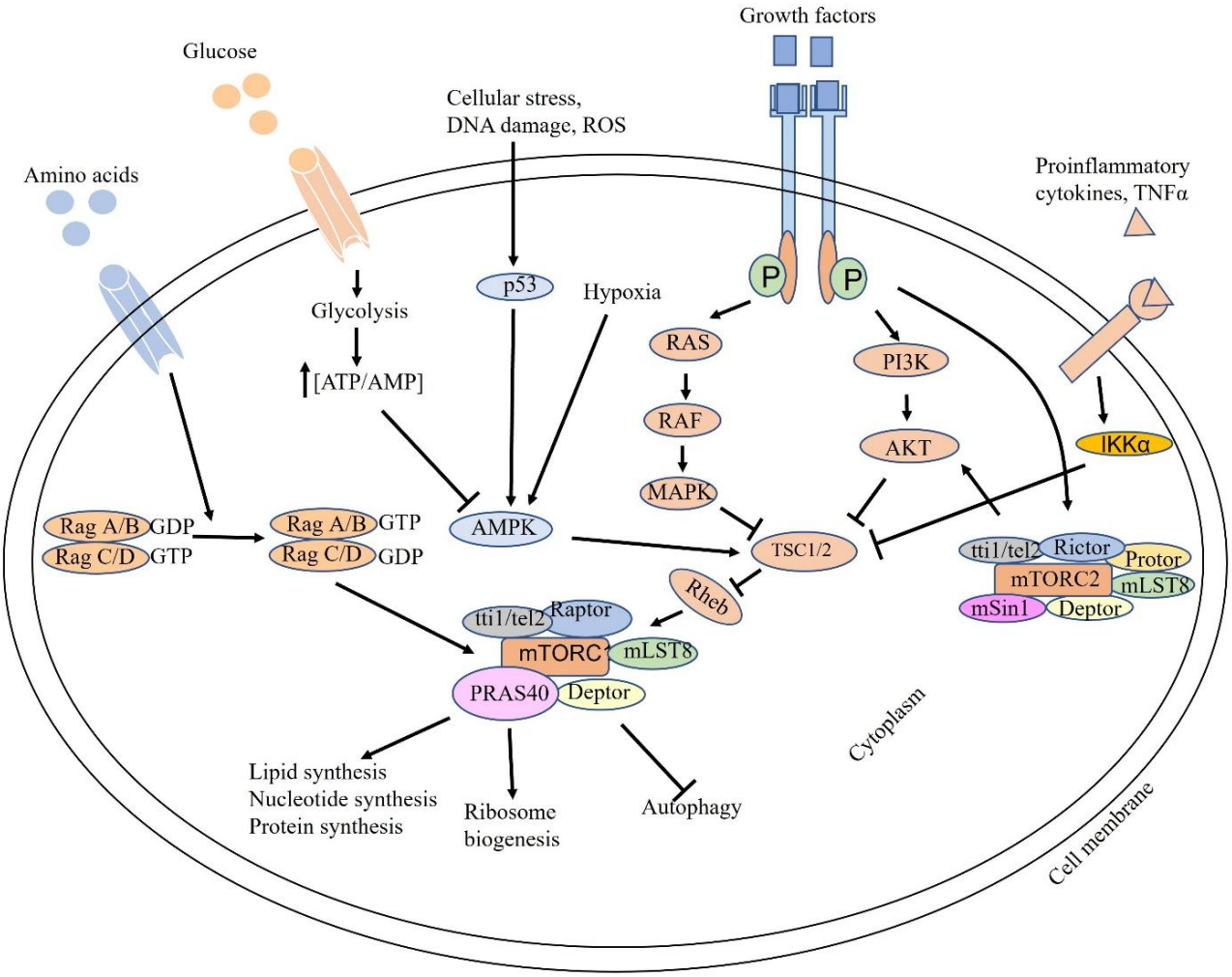

Figure 2 Overview of mTOR signaling (Kim *et al.*, 2013; Laplante & Sabatini, 2009)

tor-dependent signaling pathways, such as PI3K- serine/threonine protein kinase B(AKT) and rat sarcoma (Ras)- rapidly accelerated fibrosarcoma (Raf)- extracellular signal-regulated kinase (ERK) pathways, can inhibit Tuberous Sclerosis Complex (TSC), an important negative regulator of mTORC1 activity. Unlike mTORC1, the mTORC2 pathway remains poorly understood. However, it seems to be primarily controlled by growth factors via PI3K-AKT kinase.

Inhibition of the TSC complex (TSC1 and TSC2) activates the GTP-binding protein Ras homolog (Rheb) mTORC1 kinase (Lawrence & Nho, 2018). When glucose enters cells, glycolysis occurs, and the adenosine triphosphate (ATP)/ adenosine diphosphate (ADP) ratio is high, which causes the inhibition of adenosine monophosphate (AMP)-dependent protein kinase, thereby inhibiting the TSC complex. This triggers activation of the mTORC1 complex. In contrast, amino acids, mainly leucine and arginine, induce mTORC1 through activation of Rag GTPases. In addition to these major signaling pathways, intracellular and extracellular stresses, including DNA damage and reactive oxygen species, activate AMP-activated protein kinase (AMPK), which in turn stimulates TSC2. Hypoxia in cells also inhibits the activity of mTORC1 through activation of AMPK. Proinflammatory cytokines such as Tumor Necrosis Factor-alpha (TNFα) activate Inhibitor of κB β (Iκβ) kinase-β (IKKβ), which directly interacts with TSC1, causing mTORC1 activation (Laplante & Sabatini, 2009; Panwar *et al.*, 2023). On the other hand, extracellular matrix component, collagen type I, activates tumor suppressor phosphatase and tensin homolog (PTEN), which suppresses PI3K/AKT pro-survival pathway in fibroblast cells (Nho *et al.*, 2011; Tamura *et al.*, 1999).

Downstream target of mTOR signaling

mTORC1 controls cell growth and metabolism through protein synthesis, lipid synthesis, organelle biosynthesis, and inhibition of autophagy (**Figure 2**). The detailed mechanism by which mTORC1 regulates protein synthesis, lipid synthesis, organelle biosynthesis, and autophagy has been mentioned in the review paper of Laplante & Sabatini (2009), but in brief, they are discussed below.

Protein synthesis (mRNA biogenesis, cap-dependent translation, elongation, and ribosomal protein biogenesis) is initiated when activated mTORC1 phosphorylates eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4E-BP1) and p70 ribosomal S6 kinase 1 (S6K1). mTORC1 causes the initiation of lipid synthesis (glycolipid and cholesterol) through activation of sterol regulatory element-binding protein 1 (SREBP1), peroxisome proliferator-activated receptor-g (PPARg), and

PPARg coactivator 1(PGC1-a) transcription factors, and activation of phosphatidic acid phosphatase. PGC1-α interacts with another transcription factor, Yin-Yang 1 (YY1), and regulates mitochondrial biogenesis and oxidative phosphorylation. Autophagy, which is the invagination of intracellular components inside autophagosomes and their destruction by lysosomes, is regulated by mTORC1. mTORC1 inhibits autophagy by regulating a protein complex composed of unc-51-like kinase 1 (ULK1), autophagy-related gene 13 (ATG13), and focal adhesion kinase family interacting protein of 200 kDa (FIP200).

In contrast to mTOC1, cell survival, metabolism, and proliferation are also regulated by mTORC2 (Laplante & Sabatini, 2009). The complete activation of AKT is dependent on both phosphoinositide-dependent kinase 1 (PDK1) and mTORC2. They phosphorylate AKT at different positions on serine residues. Serum- and glucocorticoid-induced protein kinase 1 (SGK1) is activated by mTORC2. During the ablation of mTORC2, a basal level of AKT activity was observed, but the activity of SGK1 was completely reduced. Forkhead box protein O1 (FoxO1) and forkhead box O3 (FoxO3a) are phosphorylated at similar sites by SGK1 and AKT, respectively. The suppression of FoxO1 and FoxO3a phosphorylation, which activates FoxO1 and FoxO3a, may be caused by the absence of SGK1 activity in mTORC2-deficient cells. Activation of FoxO1 and FoxO3a upregulates the expression of genes involved in stress resistance, cell cycle arrest, metabolism, and apoptosis (Laplante & Sabatini, 2009).

The review paper of Laplante & Sabatini (2009) reported that TORC2 regulates the actin cytoskeleton by promoting protein kinase Ca (PKCa) phosphorylation and paxillin phosphorylation. TORC2 also induces paxillin relocalization to focal adhesions and enhances Guanosine Triphosphate (GTP) loading of Ras homolog family member A (RhoA) and Ras-related C3 botulinum toxin substrate 1 (Rac1).

Role of mTOR signaling in airway epithelial homeostasis

Lineage-tracing experiments have reported that basal stem cells give rise to ciliated and secretory club cells during homeostasis and repair (Rock *et al.*, 2009; Rock *et al.*, 2010). The lung epithelium was ablated with SO2 in mice and was allowed time to regenerate. During regeneration, the number of $Trp63^{+}$ basal cells was reduced, and secretory cells were increased. In contrast, rapamycin treatment together with SO2 significantly increased the number of basal stem cells. These results indicate that mTOR signaling negatively regulates basal stem cell proliferation.

mTOR activation was comparable to that in organoids "tracheosphere" cultures derived from murine tracheal basal stem cells. Cells arising from the basal layer exhibited intermittent activation of mTORC1 signaling, suggesting that temporary mTORC1 activity is a component of the normal differentiation mechanism in these organoids. Rapamycin induced mTORC1 inhibition dramatically lowered basal cell differentiation. Rapamycin treatment specifically reduced the growth of the tracheosphere, caused the epithelial layer to shrink, and led to the accumulation of $Trp63^{+}$ basal cells. These findings indicate that mTORC1 activity controls expansion of basal stem cells and the advancement of lineages toward secretory and ciliated cell fates (Haller *et al.*, 2017).

In a child with bronchopulmonary dysplasia, tracheal epithelial cells collected from tracheal aspirates were unable to maintain stemness, but when these cells were cultured in a selective condition (Rho/ Suppressor of Mothers against Decapentaplegic (SMAD) signaling inhibition condition), epithelial cell colonies were grown, and these colonies could be passaged three to four times. These epithelial cells are referred to as tracheal aspirate-derived (TAD) airway basal cell-like cells (BCCs). Lu *et al.* revealed that neonatal TAD BCCs did not grow after the fourth passage, but when rapamycin was added to the culture of neonatal TAD BCCs, the cells were able to grow long-term, even after the 15th passage. These results indicate a role for mTOR signaling in lung epithelial homeostasis (Lu *et al.*, 2021).

In contrast, it has been reported that during pulmonary fibrosis, including bronchiolitis obliterans syndrome, Yes-associated protein (YAP)/ transcriptional co-activator with PDZ-binding motif (TAZ) (transcription coactivator) activation stimulates mTORC1, which then activates activating transcription factor 4 (ATF 4). This activation enhances amino acid uptake and metabolism, resulting in the loss of secretory stem cell club cell identity, leading to their differentiation into AT1 like cells. This result was consistent with the results of tamoxifen-induced double conditional knockout of large tumor suppressor kinases 1 and 2 (LATS1/2) in secretory cells both in vitro and in vivo. Similarly, ablation of YAP and TAZ in dKO LATS1/2 secretory cells restored secretory cell identity and rescued the changes in lineage fate (Jeon *et al.*, 2022). These results indicate a role for mTORC1 in epithelial homeostasis during recovery from injury.

In colitis mice, apoptosis of colonocytes was observed, which compromised the epithelial barrier function. mTORC2 acts as a pro-survival stimulator Cre recombinase-mediated deletion of Rictor in intestinal epithelial cells causes apoptosis and anoikis of epithelial cells. Mechanistically, mTORC2 activates AKT, which then phosphorylates B-cell lymphoma 2 (BCL2)-associated agonist of cell death (Bad), thereby inhibiting the apoptosis of intestinal colonocytes and maintaining intestinal epithelial barrier integrity (Castro-Martinez *et al.*, 2021). Therefore, it is hypothesized that mTORC2 signaling maintains airway epithelial barrier integrity by regulating cell survival. From the above discussion, it can be concluded that balanced mTOR signaling plays an important role in airway epithelial homeostasis by regulating stem cell proliferation, differentiation, and survival.

Dysregulation of mTOR signaling in aging and diseases

Given the crucial role of mTOR signaling in airway epithelial homeostasis, dysregulation of mTOR signaling is potentially linked to aging and various diseases (**Table 1**). Organ function gradually deteriorates due to physiological and molecular changes that accompany aging (Cho & Stout-Delgado, 2020; Meiners *et al.*, 2015; Navarro & Driscoll, 2017). The ability of the lung to restructure and regenerate reduces with age. Telomere shortening, mitochondrial dysfunction, cellular senescence, and stem cell exhaustion are character-

Table 1 Role of mTOR signaling in airway epithelial homeostasis, aging, and lung diseases

Condition	Experimental models	Effect of mTOR signaling	Pathways involved	Reference
Airway epithelial homeostasis	Mice lung organoids culture. Double conditional knockout of LATS1/1 in secretory cells in vitro and in vivo. Colitis mice.	Regulation of Proliferation and differentiation of lungs stem and progenitor cells.	mTORC1 inhibition by rapamycin in organoid "tracheosphere" lowers the basal cell differentiation. YAP/TAZ → mTORC1 → ATF4 → amino acid metabolism → secretory club cells differentiation to AT1. Rictor/mTORC2→Akt→ prevents apoptosis of intestinal epithelial cells. This result suggests a role in airway epithelial barrier integrity.	(Castro-Martinez *et al.*, 2021; Haller *et al.*, 2017; Jeon *et al.*, 2022)
Aging	Airway epithelial cells of aged mice, bleomycin-treated senescent L2 cells. Club cells of aged mice. Conditional deletion of TSC2 in mesoderm-derived mesenchymal cells in mice. Accumulation of mutational loss of TSC LAM cells in mice.	mTOR hyperactivation causes cellular senescence and regenerative potential.	mTOR/PGC-1α/β upregulated → mitochondrial biogenesis, AT2 senescence. Increased mTOR activity in club cells → oxidative stress, reduced Nrf2 defense. TSC2 loss → smooth muscle accumulation →epithelial disorganization, decreased alveolarization.	(Goncharova *et al.*, 2012; Melo-Narváez *et al.*, 2020; Ren *et al.*, 2016; Smolarek *et al.*, 1998; Summer *et al.*, 2019)
Emphysema	Cigarette smoke-exposed mice. Conditional deletion of TSC1 in epithelial cells of mice.	Aberrant mTOR activation causes alveolar wall destruction.	Smoking triggers mTOR in Tc1/Tc17 cells → cytokine secretion, alveolar damage. TSC1 loss in epithelium → mTOR activation → emphysema-like pathology in mice.	(Houssaini *et al.*, 2018; Zhang *et al.*, 2019)
Acute Respiratory Distress Syndrome (ARDS)	LPS-treated mice and human bronchial alveolar cells (HBECs). Mechanical ventilator-injured patient. Oxygen-induced damaged lungs in neonatal rats.	Overactive mTORC1 worsens injury; regulated inhibition promotes recovery.	LPS → TLR4 → mTOR activation → inhibits autophagy → NF-κB inflammation. MV (ventilator) → mTORC1 activation → surfactant dysfunction, ventilator-induced lung injury (VILI). AMPK/CGRP → inhibit mTOR → induce autophagy → tissue recovery.	(Hu *et al.*, 2016; Lee *et al.*, 2021; Brower *et al.*, 2000; Tremblay & Slutsky, 2006; Wang *et al.*, 2024)
Cancer (e.g., NSCLC, carcinoid tumors)	Typical carcinoid and atypical carcinoid tumors in patients.	Chronic mTOR activation promotes tumorigenesis via the PI3K/AKT/mTOR axis.	mTOR, TSC1/2, PTEN, and PIK3CA mutations → mTOR upregulation→ enhances G1–S transition → genomic instability, proliferation.	(Brown *et al.*, 1994; Tan, 2020; Zhang & Wang, 2017)

istics linked to aging (Cho & Stout-Delgado, 2020; Meiners *et al.*, 2015). Cell senescence is defined as the sustained cessation of growth. Senescent cells exhibit a diverse phenotype, which includes permanent inhibition of the cell cycle via the tumor suppressor p53 (TP53) and/or p16/retinoblastoma (Rb) pathways, larger cell size, changed cellular morphology, resistance against apoptosis, and a distinct secretory phenotype known as the senescence-associated secretory phenotype (SASP) (Celli & MacNee, 2004).

In aged mice, the airway epithelial cells become senescent. In old mice, AT2 cells showed increased levels of the senescent markers p21 and p16 compared to young mice. Mitochondrial biogenesis was increased in the alveolar epithelial cells of these mice, as evidenced by the increased phosphorylation of mTORC1 and p70S6K compared to that in young mice. Mitochondrial biogenesis was evidenced by an increased mitochondrial mass, indicated by an approximately two-fold elevation of TOM20, a mitochondrial outer

membrane protein, which resulted from activation of the mTORC1/PGC-1 axis. These markers also increased in rat senescent L2 cells induced by bleomycin treatment (Summer *et al.*, 2019).

In addition to AT2 cells, in old mice, increased oxidative stress, impaired antioxidant defense (lower Nrf2 activity), and enhanced mTOR activity in airway club cells were observed compared to those in young mice. Increased oxidative stress was noticed by increased reactive oxygen species (ROS) production, which was due to an increased number of mitochondria and cellular respiration (Melo-Narváez *et al.*, 2020). The loss of TSC2 expression and function in the lung, which negatively regulates mTOR, can result in the loss of epithelial structure and the accumulation of smooth muscle cells (Goncharova *et al.*, 2012; Ren *et al.*, 2016; Smolarek *et al.*, 1998). Airway smooth muscle cells in elderly persons increase the expression of senescent markers, p53 and p21, and telomere-associated foci in whole lungs, including airway epithelial cells (Aghali *et al.*, 2022). Taken together, mTOR hyperactivation is a major cause of age-related pulmonary decline because it promotes cellular senescence, lowers regenerative potential, and impairs progenitor cell function.

Emphysema is defined as the aberrant, long-term expansion of air gaps distal to the terminal bronchioles and alveolar wall disintegration (Bentaher *et al.*, 2025). Smoking is the most common risk factor for emphysema (He *et al.*, 2023). Cigarette smoke-exposed mice exhibited enlarged alveolar spaces, thinner alveolar walls, cilia lodging, inflammatory cell infiltration, and significant destruction of alveoli compared with air-exposed mice. Tc1 and Tc17 cells, referred to as IFN-γ-producing and interleukin -17 (IL-17)-producing CD8+ T cells, respectively, were increased in smoke-exposed mice. Rapamycin treatment significantly decreases the number of these cells, leading to emphysema through the secretion of cytokines (Zhang *et al.*, 2019). Conditional deletion of TSC1 in airway epithelial cells causes mTOR signaling (mTORC1 and mTORC2) activation, which results in destruction of the alveolar wall and emphysema-like pathology in mice without changes in telomere length (Houssaini *et al.*, 2018). Altogether, it has been reported that the mTOR signaling pathway controls the emphysema-like phenotype in lung tissues.

Acute respiratory distress syndrome (ARDS) is a fatal condition. It is characterized by non-compliant or "stiff" lungs and inadequate oxygenation. Diffuse alveolar damage and capillary endothelial injury are associated with these conditions (Confalonieri *et al.*, 2017). In LPS-treated mice and human bronchial alveolar cells (HBECs), p-mTOR and phosphorylated Ribosomal Protein S6 (p-RPS6) were upregulated and the autophagy-related marker LC3B was downregulated, suggesting that mTOR signaling inhibits autophagy. LC3B knockdown increased inflammation in HBECs. Conditional deletion of mTOR in airway epithelial cells in mice reduces inflammation, thereby causing acute lung injury. (Hu *et al.*, 2016). These results suggest that mTOR signaling plays a role in ARDS. Supportive therapy with mechanical ventilation (MV) is the only treatment for ARDS patients. However, MV can worsen the existing injury of the lungs, known as ventilator-induced lung injury (VILI). Limiting lung distention reduces the mortality rates in ARDS patients (Brower *et al.*, 2000; Tremblay & Slutsky, 2006).

In mice injured by injurious force during mechanical ventilation, mTORC1 is highly activated, as evidenced by P-S6 in the airway epithelium, including alveolar epithelial cells. These mice were critically ill and developed ARDS. Conditional deletion of TSC2 in mice did not affect lung compliance, but mTOR activity was increased, as detected by immunohistochemical staining. In contrast, TSC2 deleted mice faced volutrauma, and atelectrauma exhibited decreased lung compliance, indicating that injurious force caused increased levels of mTORC1, which were responsible for developing ARDS, but MV-treated ARDS patients with diffuse alveolar damage caused more mTOR activation than ARDS patients only. These results suggested that MV activates mTOR. Rapamycin treatment ameliorates lung damage during injurious mechanical ventilation and improves surfactant dysfunction (Lee *et al.*, 2021).

Under hyperoxic conditions, a frequent consequence of ARDS management, lung tissues are injured. Under these conditions, AMPK is overexpressed in airway epithelial cells and inhibits mTOR and TP53, thereby causing autophagy. Autophagy clears damaged cells, thereby recovering from injury. Calcitonin gene-related peptide (CGRP) augments this process, thereby ameliorating injury (Wang *et al.*, 2024). Taken together, LPS-induced lung injury, ventilator-induced lung injury (VILI), and epithelial dysfunction are exacerbated by mTORC1 hyperactivation, whereas cytoprotective autophagy and tissue healing are promoted by controlled mTORC1 suppression through the AMPK or CGRP pathways. Pharmaceutically modifying the AMPK–mTOR–autophagy axis thus becomes a viable treatment approach that may be used in conjunction with MV to lessen the damage in acute respiratory distress syndrome.

Abnormal mTOR activation through the PI3K/AKT axis can prolong the cell cycle transition from the G1 to S phase, which allows for the accumulation of mutations in the cell through genomic instability, leading to the emergence of a wide range of tumors (Brown *et al.*, 1994; Zhang & Wang, 2017). DNA Sequence analysis and immunostaining of patient tissues revealed that specific genetic alterations, such as missense mutations in mTOR exon 48 (c.6667C>T) and tuberous sclerosis complex (TSC) 1 exon 21 (c.2765G>A), were related to mTOR expression in typical carcinoid and atypical carcinoid tumors and may be the driver gene for carcinoid (Zhang & Wang, 2017). Similarly, Exon 9 mutations (E545K and E542K) in PK3KCA, loss of PTEN expression by promoter methylation, AKT1 exon 4 mutation (E17K), and epidermal growth factor receptor (EGFR) mutations have been observed in some patients with non-small cell lung cancer (NSCLC) (Tan, 2020), which may result from aberrant activation of mTOR-like carcinoids. Thus, from the above results, it is concluded that upregulation of the PI3K/AKT/mTOR pathway can cause various lung cancers.

Therapeutic agents/drugs used for dysregulated mTOR

mTOR activation is considered to be a central pathway that causes aging, emphysema, ARDS, and cancer. By inhibit-

ing mTORC1 (and, to a lesser extent, mTORC2) signaling, mTOR inhibitors, including rapamycin and its analogs (everolimus and temsirolimus), have a wide range of pharmacological effects, including immunosuppression. Rapamycin inhibits cellular senescence, decreases mTOR activity in aging lungs, and reduces age-associated collagen deposition in mouse models (Calhoun *et al.*, 2016). Lung cell senescence and emphysematous alterations in emphysema are caused by mTOR hyperactivation, whereas low-dose rapamycin reverses senescence-associated secretory phenotypes, protects against emphysema in transgenic mice (Houssaini *et al.*, 2018), and reduces Tc1/Tc17-driven inflammatory responses in mice subjected to cigarette smoke (Zhang *et al.*, 2019). In ARDS/ALI, rapamycin increases autophagy to maintain alveolar and vascular health and improve performance in LPS-induced models (Qin *et al.*, 2020), although in some settings, it can promote injury and apoptosis through STAT1 activation (Fielhaber *et al.*, 2012). Rapamycin and its analogs are being evaluated clinically for non-small cell lung cancer (NSCLC), but their efficiency appears to be limited by the feedback activation of AKT, which may necessitate the use of combination therapies (Memmott & Dennis, 2010).

Based on the above discussion, it can be concluded that therapeutic efficacy depends on the disease state. It also impairs tissue repair and causes metabolic disturbances (Houde *et al.*, 2010; Weinreich *et al.*, 2011). In this case, intermittent or low doses were effective. Therefore, chronic inhibition could be avoided to prevent impaired tissue regeneration. Treatment duration and dosing strategies can also be effective strategies for using rapamycin. Recent studies have shown that rapamycin-loaded nanoparticles, including solid lipid nanoparticles used for inhalation, enhance pulmonary drug delivery, thus minimizing systemic toxicity and metabolism. In animal studies on ARDS, metformin enhanced experimental lung damage and survival rates by reducing oxidative damage and pulmonary inflammation. Metformin can activate AMPK-1 isoforms and improve LPS-induced endothelial permeability and pulmonary edema (Wang *et al.*, 2023). The possible use of next-generation mTOR antagonists, such as vistusertib, to treat acute respiratory distress syndrome (ARDS) and lung cancer is being intensively studied. These drugs target mTORC1/2 complexes, which are linked to tumor growth and resistance to standard treatments in lung cancer, especially NSCLC (Middleton *et al.*, 2025).

Conclusion

To preserve the delicate balance of lung epithelial function, mTOR signaling combines cellular reactions with external stimuli. Although its activity supports homeostatic functions, such as cell proliferation, differentiation, repair, and cell survival, its dysregulation is a typical feature of a variety of pulmonary disorders. Dysregulated mTOR activity during aging makes the lungs more vulnerable to long-term damage by accelerating senescence and impairing epithelial repair. While overactive mTOR causes endothelial and epithelial malfunctions in acute ARDS, exacerbating inflammatory damage, excessive mTOR activation in emphysema disturbs epithelial renewal and encourages alveolar degradation. In contrast, mTOR signaling promotes unchecked development and metabolic reprogramming, thereby resulting in cancer. At the same time, pharmacological inhibition of mTOR explains the therapeutic potential, but must be carefully calibrated to inhibit the negative effects on tissue repair and metabolic homeostasis. Developing targeted treatment approaches that maintain epithelial regeneration while reducing pathological remodeling in lung illnesses would require a deeper understanding of cell type-specific mTOR regulation and disease stage-dependent signaling dynamics.

Research gaps and future research direction

Although there is evidence of the role of mTORC1 signaling in airway epithelial homeostasis (Haller *et al.*, 2017), but for mTOC2 remains incompletely defined. Therefore, future research should focus on these issues. In contrast, the cell-type-specific functions of mTORC1 and mTORC2 within distinct airway epithelial stem and progenitor populations, including basal cells, club cells, and alveolar type II cells, have not been fully delineated, particularly under conditions of homeostasis (Castro-Martinez *et al.*, 2021; Haller *et al.*, 2017; Jeon *et al.*, 2022). Although mTOR hyperactivation has been linked to epithelial senescence, emphysema, and lung injury, the upstream molecular triggers that drive sustained mTOR activation during physiological aging are not fully understood (Houssaini *et al.*, 2018; Melo-Narváez *et al.*, 2020). Identifying the upstream metabolic, inflammatory, and mechanical cues that sustain mTOR hyperactivation during aging, emphysema, and acute lung injury will further clarify disease initiation and progression (Houssaini *et al.*, 2018; Hu *et al.*, 2016; Lee *et al.*, 2021).

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Author contribution ZK: conceptualization, visualization, investigation, data curation, analysis, writing-original draft, writing-review and editing; SS: visualization; SH: writing-review and editing.

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