

Autophagy-epithelial-mesenchymal transition crosstalk in acute respiratory distress syndrome: Mechanistic insights and therapeutic perspectives (Review)

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Abstract. Acute respiratory distress syndrome (ARDS) is a life-threatening pulmonary disorder frequently encountered in intensive care units, characterized by diffuse alveolar damage, intense inflammatory infiltration and progressive fibrotic remodeling. Among the mechanisms driving fibrosis, the epithelial-mesenchymal transition (EMT) has gained increasing recognition as a key contributor to the generation of fibroblasts and extracellular matrix deposition. Autophagy, a tightly regulated intracellular degradation and recycling process, serves a context-dependent role in EMT regulation and lung injury. While basal autophagy supports pulmonary

cellular homeostasis, dysregulated or excessive autophagy may exacerbate tissue injury and maladaptive repair. The literature has previously highlighted both classical macroautophagy and selective autophagy pathways, including mitophagy, endoplasmic reticulum-selective autophagy and ferritinophagy, as modulators of EMT dynamics and fibrotic outcomes. However, the mechanistic associations between specific autophagy subtypes and EMT in ARDS remain poorly defined and occasionally contradictory. In the present review, current evidence on autophagy-EMT crosstalk in ARDS is critically appraised, conceptual gaps and controversies are identified and further potential mechanistic frameworks and research priorities are summarized. Such investigation may help inform the rational targeting of autophagy pathways in future ARDS therapies.

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Abbreviations: 4-PBA, 4-phenylbutyric acid; ALI, acute lung injury; AMPK, AMP-activated protein kinase; ATL3, atlastin GTPase 3; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transition; ER, endoplasmic reticulum; ER-phagy, ER-selective autophagy; FAM134B, family with sequence similarity 134 member B; FTH, ferritin heavy chain; HIF-1 α , hypoxia-inducible factor 1 α ; ICU, intensive care unit; IRE1, inositol-requiring enzyme 1; LPS, lipopolysaccharide; NCOA4, nuclear receptor coactivator 4; Parkin, parkin RBR E3 ubiquitin protein ligase; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; RTN3L, reticulon 3 long isoform; SEC62, SEC62 preprotein translocation regulator; Snail, zinc-finger transcription factor SNAI1; SQSTM1/p62, sequestosome 1; ULK1, unc-51 like autophagy activating kinase 1; UPR, unfolded protein response; XBP1, X-box binding protein 1

Key words: acute respiratory distress syndrome, pulmonary fibrosis, epithelial-mesenchymal transition, selective autophagy, therapeutic targets

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1. Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening respiratory disorder with high mortality rates, affecting ~10% of intensive care unit admissions worldwide (1-4). Despite advances in ventilatory strategies and critical care, mortality remains between 35-46%. ARDS arises from a complex interplay of numerous concurrent injuries, inflammatory responses and dysregulated coagulation pathways, affecting both the pulmonary system and the whole body. As shown in Fig. 1, ARDS progression involves a cascade of pathological events, including alveolar-capillary barrier disruption, inflammatory cell recruitment, and increased vascular permeability, leading to pulmonary edema and subsequent hypoxemia. Furthermore, early fibroproliferative responses are key determinants of lung

remodeling and prognosis. A hallmark of ARDS is the early onset of fibroproliferative changes in the lung, which are associated with poor outcomes (5). These fibroproliferative responses are among the earliest events in ARDS and highlight the need to understand molecular drivers of lung remodeling and to develop novel therapeutic strategies targeting early pathogenic events.

Autophagy, recognized by the 2016 Nobel Prize in Physiology or Medicine awarded to Ohsumi (6), is a fundamental cellular quality-control process responsible for degrading damaged organelles, aggregated proteins and invading pathogens (7,8). It exists in both non-selective and selective forms, such as mitophagy, ferritinophagy and reticulophagy. Dysregulated autophagy has been implicated in a number of pathological conditions, including acute lung injury (ALI); however, its specific and context-dependent roles in ARDS pathogenesis remain incompletely understood.

The epithelial-mesenchymal transition (EMT) is an additional key biological process contributing to tissue remodeling and fibrosis. In the lung, EMT of epithelial or endothelial cells can generate fibroblasts that deposit extracellular matrix (ECM), contributing to fibrosis (9). In the present study, the term EMT is used broadly to include both the classical EMT in epithelial cells and the endothelial-to-mesenchymal transition (EndMT) in endothelial cells. Emerging evidence has indicated that autophagy can modulate EMT, either promoting or restraining it, depending on the context and type of selective autophagy involved (10-13). However, the molecular crosstalk between autophagy and EMT in ARDS is incompletely understood and existing studies often examine these processes in isolation (14-16).

The present review assesses current knowledge regarding the interplay between classical and selective autophagy (mitophagy, ferritinophagy and reticulophagy) and EMT in ARDS, highlighting converging and diverging findings and proposing a hypothesis-driven framework to guide future research. Through focusing on the intersection of these pathways, the present review provides a framework beyond descriptive summaries and toward mechanistic and translational perspectives, which may inform rational targeting of autophagy pathways in future ARDS therapies.

2. Literature search and study selection

A comprehensive literature search was conducted to identify studies relevant to autophagy-EMT crosstalk in ARDS and pulmonary fibrosis. The databases PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Web of Science (<https://www.webof-science.com/>) were systematically searched for articles published in English between January 2000 and March 2025.

The search strategy combined medical subject heading terms and free-text keywords, including but not limited to: 'acute respiratory distress syndrome', 'acute lung injury', 'pulmonary fibrosis', 'epithelial-mesenchymal transition', 'endothelial-mesenchymal transition', 'autophagy', 'macroautophagy', 'mitophagy', 'ferritinophagy' and endoplasmic reticulum (ER)-selective autophagy ('ER-phagy'). Boolean operators ('AND' and 'OR') were applied to refine the search.

Studies were included if they met one or more of the following criteria: i) Investigated autophagy or selective autophagy subtypes in ARDS or ALI models; ii) examined EMT

or EndMT in the context of lung injury or pulmonary fibrosis; or iii) provided mechanistic insights into autophagy-EMT interactions derived from other disease models (such as cancer, fibrotic or metabolic disorders), provided that the reported mechanisms were mechanistically linked to processes known to contribute to ARDS, including inflammation, epithelial or endothelial injury, and alveolar-capillary barrier dysfunction. Reviews, original experimental studies and translational research articles were considered.

Studies were excluded if they: i) Lacked mechanistic relevance to autophagy or EMT; ii) were not available in full text; or iii) were published in languages other than English. Article screening and study selection were independently performed by two authors. Any discrepancies were resolved through discussion until a consensus was reached. Given the heterogeneity of experimental models and outcomes, the present research was designed as a narrative review and no formal meta-analysis was performed.

3. Role of autophagy in ARDS

Macroautophagy in ARDS: Mechanisms and evidence. Macroautophagy, a lysosome-dependent degradation pathway, serves a stage- and context-dependent role in the pathogenesis of ARDS. During the early phase of injury, moderate autophagy activation can limit inflammatory damage, maintain epithelial-endothelial barrier integrity and support cellular homeostasis. By contrast, excessive or prolonged autophagy may induce autophagic cell death and promote fibrotic remodeling, underscoring the need for precise temporal and quantitative regulation (17).

Macroautophagy proceeds through initiation, phagophore formation, autophagosome maturation and lysosomal degradation, as shown in Fig. 2 (18), which illustrates key regulatory pathways, including mTOR, unc-51 like autophagy activating kinase 1 (ULK1), AMP-activated protein kinase (AMPK) and PI3K/AKT, which integrate environmental and cellular stress signals to modulate autophagic activity during ARDS. Under healthy conditions, temporal regulation of these pathways limits inflammation and prevents fibrotic remodeling (19).

In ARDS models, mTOR-centered regulation has been extensively studied (20-22). Rapamycin-mediated mTOR inhibition enhances autophagy and alleviates lipopolysaccharide (LPS)-induced lung injury, whereas pharmacological blockade of autophagy by 3-methyladenine (3-MA) generally aggravates acute-phase pathology (21). Notably, in chronic or fibrotic contexts, 3-MA may attenuate tissue injury by limiting maladaptive or excessive autophagy, suggesting that the effects of autophagy modulation are highly context-dependent, varying with disease stage, target cell populations and timing of intervention (23).

Cell-type-specific roles further complicate this. In macrophages, sirtuin 6 promotes M2 polarization and suppresses inflammatory responses partially through autophagy activation (24-27). Dioscin enhances alveolar macrophage autophagy, mitigating silica-induced lung injury and fibrosis (28). Mesenchymal stem cell-derived exosomes demonstrate cargo-dependent effects, as microRNA-377-3p-containing exosomes promote protective autophagy (29), whereas heparanase-rich exosomes may exacerbate fibrotic remodeling (30).

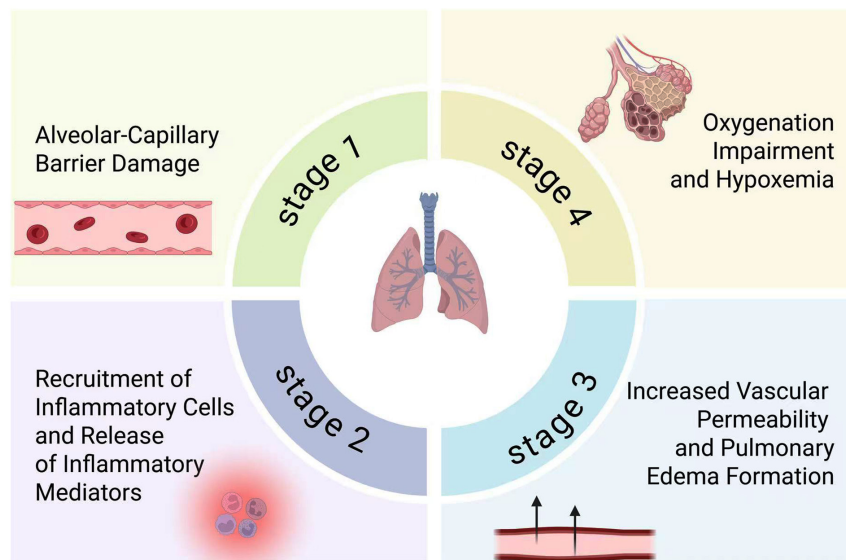


Figure 1. Mechanistic overview of ARDS progression. Schematic illustrates the major pathological events in ARDS, organized into four interrelated stages surrounding a central lung diagram. Stage 1: Alveolar-capillary barrier damage. Structural disruption of the alveolar-capillary interface allows leakage of plasma and proteins into alveoli (ARDS-specific). Stage 2: Recruitment of inflammatory cells and mediator release. Neutrophils, macrophages and cytokines accumulate, amplifying local inflammation (ARDS-specific). Stage 3: Increased vascular permeability and pulmonary edema formation. Fluid extravasation into alveolar and interstitial spaces (ARDS-specific). Stage 4: Oxygenation impairment and hypoxemia. Impaired gas exchange results in reduced oxygen saturation (ARDS-specific). Arrows indicate the direction of pathological progression. Early fibroproliferative responses, shown schematically, highlight the onset of tissue remodeling, a hallmark of poor prognosis. ARDS, acute respiratory distress syndrome.

Natural compounds such as astragaloside IV have also been investigated. In ARDS cell models, astragaloside IV inhibits excessive autophagy, reduces oxidative stress and preserves epithelial barrier integrity (31). While such agents are attractive for their relative safety and multitarget activity, current evidence is largely preclinical, with limited data regarding long-term efficacy or clinical applicability.

Overall, the effects of macroautophagy depend on activation intensity, timing and cellular context, with both protective and maladaptive roles reported. Existing studies are limited by heterogeneous models and predominantly short-term endpoints. Future research should therefore prioritize standardized ARDS models, longitudinal analyses and targeted modulation strategies, particularly within immune cell populations and stem-cell-derived vesicle systems. Key molecular targets, experimental models and main conclusions are summarized in Table I.

Ferritinophagy in ARDS: Functions and implications.

Ferritinophagy, a selective autophagy pathway mediated by nuclear receptor coactivator 4 (NCOA4), degrades ferritin to release stored intracellular iron. While ferritin serves as the main cytosolic iron reservoir and is key in iron homeostasis, dysregulated ferritinophagy can lead to iron overload, driving ferroptosis, a regulated, iron-dependent form of cell death implicated in ARDS pathogenesis (32,33).

Moderate iron availability supports reactive oxygen species (ROS) production, contributing to antimicrobial defense. However, excessive iron accelerates lipid peroxidation, ferroptosis and prolonged tissue injury (34). Pulmonary iron accumulation has been observed in both patients with ARDS and murine models, correlating with oxidative stress, lipid peroxidation and fibrotic remodeling (35). Therapeutic

interventions using iron chelators such as deferoxamine can attenuate fibrosis by reducing pulmonary iron burden, although their long-term efficacy and cell-type-specific effects, particularly on fibroblasts and macrophages, remain to be fully elucidated (36).

A number of regulators of ferritinophagy have been investigated in ARDS models. Hecpudin alleviates LPS-induced ARDS by suppressing ferroptosis through downregulation of transferrin receptor 1 and upregulation of ferritin heavy chain (FTH), with FTH being central to its protective effect (37). Conversely, NCOA4 actively promotes ferritinophagy, elevating free iron, enhancing ROS generation and triggering lipid peroxidation-mediated cell death (38). Pharmacological inhibition of NCOA4, as demonstrated with melatonin treatment, reduces ferritinophagy in alveolar macrophages, limits iron release and improves outcomes in septic ARDS (39). Similarly, Yes1 associated transcriptional regulator (YAP1) suppresses ferritinophagy, lowers intracellular free iron, reduces ROS production and alleviates lung injury in sepsis-induced ALI models (40).

Collectively, these studies indicate that NCOA4-driven ferritinophagy is the association between iron metabolism dysregulation and ferroptotic cell death, perhaps contributing to fibrosis in ARDS. Its effects are context-dependent, potentially varying with injury stage, pulmonary cell type and systemic iron status. Modulation of ferritinophagy, either through endogenous regulators (hepcidin and YAP1) or pharmacological agents (melatonin and iron chelators), represents a promising therapeutic approach. Future research should therefore prioritize safer, more effective iron-targeted therapies, explore cell-type-specific interventions and optimize pulmonary delivery strategies (such as inhalation) to maximize local efficacy while minimizing systemic toxicity. Key molecules,

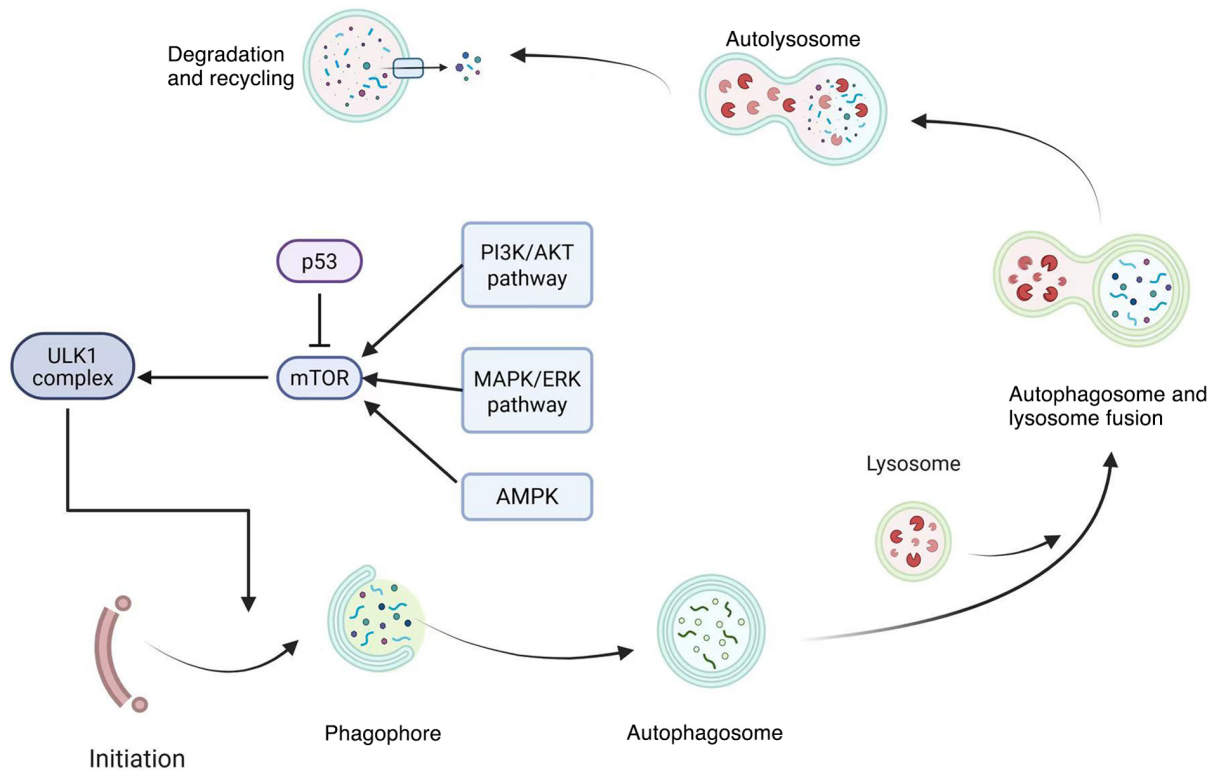


Figure 2. Macroautophagy process and key regulatory pathways. Diagram showing the sequential steps of autophagy and their upstream molecular regulators. Autophagy process: i) Initiation; ii) phagophore formation; iii) autophagosome maturation; iv) autophagosome-lysosome fusion; v) autolysosome; and vi) degradation and recycling (general mechanism). Regulatory pathways: mTOR integrates upstream signals from PI3K/AKT and MAPK/ERK (activators) and AMPK (inhibitor). ULK1 complex mediates phagophore nucleation downstream of mTOR. p53 modulates autophagy indirectly under stress conditions. Contextual relevance: Moderate autophagy during early ARDS protects alveolar epithelial and endothelial cells, maintaining barrier integrity (ARDS-specific), whereas excessive or prolonged activation may trigger autophagic cell death and fibrosis (partially extrapolated from other models). Arrows indicate activation or inhibition. ARDS, acute respiratory distress syndrome; ULK1, unc-51-like kinase 1; AMPK, AMP-activated protein kinase.

ferritinophagy states, molecular targets, experimental models and main conclusions are summarized in Table II.

Mitophagy in ARDS: Mitochondrial quality control. Mitophagy, the selective autophagic removal of damaged or excess mitochondria, is a key quality control mechanism that preserves mitochondrial function and cellular homeostasis in lung tissue. Proper regulation of mitophagy is key in maintaining alveolar epithelial and immune cell function, whereas dysregulated mitophagy contributes to mitochondrial dysfunction, excessive ROS production and inflammatory injury, collectively exacerbating ARDS pathogenesis.

Mechanistically, the PTEN-induced kinase 1 (PINK1)/parkin RBR E3 ubiquitin protein ligase (Parkin) signaling pathway serves as the central axis orchestrating mitophagy in response to mitochondrial damage. In ARDS models, polydatin, a natural polyphenol, activates Parkin-dependent mitophagy, preventing LPS-induced mitochondrial apoptosis and attenuating lung injury (41). Similarly, sestrin 2 enhances mitophagy in alveolar macrophages through the PINK1/Parkin pathway, offering protection against LPS-induced ALI and ARDS (42).

Beyond canonical regulators, additional modulators have been identified. In cecal ligation and puncture sepsis models, resveratrol restores mitochondrial function by modulating phospholipid scramblase 3, thereby reducing alveolar injury (43). The transcription factor RUNX family

transcription factor 1 promotes mitophagy through upregulation of adaptor proteins p62 and BCL2 interacting protein 3 like, preserving mitochondrial integrity and limiting epithelial cell injury and inflammation (44). Resveratrol additionally exerts dual benefits by activating PINK1/Parkin-mediated mitophagy while concurrently suppressing NLR family pyrin domain containing 3 inflammasome activation, further facilitating lung tissue recovery (45).

These findings underscore mitophagy as a context-dependent regulator of mitochondrial quality and inflammatory responses in ARDS. The effects may vary with disease stage, cell type and injury severity, highlighting the need to define temporal and cell-type-specific dynamics. Translationally, targeted mitophagy modulation, potentially combined with anti-inflammatory or antifibrotic strategies, represents a promising therapeutic approach. Future studies should therefore focus on mechanistic characterization, optimal timing of intervention and combination therapies to maximize clinical benefit. Key molecular regulators, experimental models and main outcomes of mitophagy in ARDS are summarized in Table III.

ER-phagy in ARDS: ER homeostasis. ER-phagy is a specialized form of autophagy that selectively degrades excess or damaged ER components to maintain ER homeostasis. The ER is key in protein folding, calcium storage and lipid and carbohydrate metabolism. Under stress conditions, accumulation

Table I. Roles and molecular mechanisms of macroautophagy in ARDS.

First author, year	Drug/molecule	Autophagy state	Main molecular targets and pathways	Experimental model	Main conclusion	(Refs.)
Qin <i>et al.</i> , 2020	Rapamycin	Activates	mTOR inhibition; ULK1-VPS34 activation	LPS-induced ALI rat model (ARDS-specific)	Enhances autophagy and attenuates inflammatory lung injury	(21)
Wang <i>et al.</i> , 2023	WWOX	Activates	mTOR-ULK1 signaling axis	LPS-induced ALI cells and mouse models (ARDS-specific)	Promotes protective autophagy and reduces lung inflammation	(23)
Wei <i>et al.</i> , 2020	MicroRNA-377-3p (MSC-derived exosomes)	Activates	RPTOR (mTOR complex component)	LPS-induced ALI mouse model (ARDS-specific)	Enhances protective autophagy and mitigates ARDS severity	(29)
Liu <i>et al.</i> , 2023	SIRT6	Activates	ERK1/2 signaling pathway	LPS-treated A549 cells and a murine ARDS model (ARDS-specific)	Suppresses inflammation and alleviates ARDS	(27)
Wang <i>et al.</i> , 2022	SIRT6	Activates	Macrophage M2 polarization	LPS-induced BMDMs and mouse ARDS model (ARDS-specific)	Reduces inflammatory injury through immunomodulatory autophagy	(24)
Du <i>et al.</i> , 2019	Dioscin	Activates	Alveolar macrophage autophagy	CS-induced silicosis in mouse ARDS model (pulmonary relevant)	Attenuates lung injury and fibrosis through macrophage autophagy	(28)
Liu <i>et al.</i> , 2020	Astragaloside IV	Inhibits	Oxidative stress and inflammatory signaling	LPS-induced ARDS cell model (ARDS-specific)	Prevents maladaptive autophagy and preserves epithelial barrier integrity	(31)

ARDS, acute respiratory distress syndrome; LPS, lipopolysaccharide; ALI, acute lung injury; CS, crystalline silica; ULK1, unc-51 like autophagy activating kinase 1; RPTOR, regulatory-associated protein of mTOR; SIRT6, sirtuin 6; WWOX, WW domain-containing oxidoreductase.

Table II. Roles and molecular mechanisms of ferritinophagy in ARDS.

First author, year	Drug/molecule	Ferritinophagy state	Main molecular targets and pathways	Experimental model	Main conclusion	(Refs.)
Jiao <i>et al.</i> , 2022	Hepcidin	Inhibits	FTH and TFR1	LPS-induced ARDS mouse model (ARDS-specific)	Limits iron release and ferroptosis, alleviating ARDS	(37)
Zhou <i>et al.</i> , 2022	NCOA4	Activates	Ferritin degradation; free iron release	Ionizing radiation-treated intestinal epithelial cells	Excessive ferritinophagy induces iron-dependent cell death	(38)
Xu <i>et al.</i> , 2024	Melatonin	Inhibits	NCOA4 and ferritin axis	Septic ARDS mouse model and alveolar macrophages (ARDS-specific)	Reduces iron overload and ferroptosis, improving septic ARDS outcomes	(39)
Zhang <i>et al.</i> , 2022	YAP1	Inhibits	Ferritin stability; intracellular free iron	Sepsis-induced ALI mouse model (pulmonary relevant)	Suppresses ROS generation and attenuates lung injury	(40)

ARDS, acute respiratory distress syndrome; NCOA4, nuclear receptor coactivator 4; FTH, ferritin heavy chain; TFR1, transferrin receptor 1; LPS, lipopolysaccharide; ROS, reactive oxygen species; YAP1, Yes1 associated transcriptional regulator.

Table III. Roles and molecular mechanisms of mitophagy in ARDS.

First author, year	Drug/molecule	Mitophagy state	Main molecular targets and pathways	Experimental model	Main conclusion	(Refs.)
Li <i>et al.</i> , 2019	Polydatin	Activates mitophagy	Parkin-mediated mitochondrial clearance	LPS-induced ARDS mouse model	Protects against mitochondrial apoptosis and lung injury	(41)
Wu <i>et al.</i> , 2021	Sestrin 2	Activates mitophagy	PINK1/Parkin pathway	LPS-induced mouse ALI model	Preserves mitochondrial homeostasis and attenuates ARDS	(42)
Wang <i>et al.</i> , 2021	Resveratrol	Activates mitophagy	PLSCR-3-mitochondrial signaling	CLP-induced septic ARDS mouse model	Restores mitochondrial function and mitigates lung injury	(43)
Tang <i>et al.</i> , 2023	RUNX1	Activates mitophagy	p62 and BNIP3L upregulation	LPS-induced ALI mouse model	Limits epithelial injury and inflammatory responses	(44)
Wu <i>et al.</i> , 2024	Resveratrol	Activates mitophagy	PINK1/Parkin, NLRP3 inflammasome inhibition	LPS-induced ALI mouse model	Coordinates mitophagy activation with inflammasome suppression	(45)

RUNX1, Runt-related transcription factor 1; PINK1, PTEN-induced kinase 1; Parkin, parkin RBR E3 ubiquitin protein ligase; PLSCR-3, phospholipid scramblase 3; BNIP3L, BCL2 interacting protein 3 like; NLRP3, NLR family pyrin domain containing 3; LPS, lipopolysaccharide; ALI, acute lung injury; CLP, cecal ligation and puncture; ARDS, acute respiratory distress syndrome.

of misfolded proteins triggers the unfolded protein response (UPR), an adaptive signaling pathway that increases chaperone production and reduces protein load (46). Notably, UPR activation directly interfaces with ER-phagy, ensuring selective clearance of dysfunctional ER fragments and alleviating cellular stress (12).

In ALI and ARDS, ER stress contributes to epithelial apoptosis and inflammation, exacerbating lung injury. ER-phagy mitigates these effects by restoring ER homeostasis, reducing apoptosis and modulating inflammatory signaling (47). A number of ER-phagy receptors, including family with sequence similarity 134 member B (FAM134B), reticulon 3 long isoform (RTN3L), SEC62 preprotein translocation regulator (SEC62) and atlastin GTPase 3 (ATL3), mediate these protective effects and may serve as potential therapeutic targets (48).

Emerging evidence suggests ER-phagy also influences immune cell function (47,49-51). In ARDS, macrophage polarization and inflammatory responses are tightly regulated by ER-phagy, which may indirectly affect EMT and fibrosis. Dysregulated ER-phagy could exacerbate inflammation, impair host defense and promote maladaptive remodeling. Conversely, therapeutic modulation of ER-phagy may enhance resolution of lung injury and support tissue repair (47).

Although preclinical studies have highlighted the protective role of ER-phagy, the temporal dynamics, receptor-specific functions and cell-type specificity remain incompletely understood (47,52-54). Future research should therefore investigate: i) How ER-phagy influences immune cell subsets, particularly macrophages; ii) the interactions between ER-phagy and other selective autophagy pathways (such as mitophagy and ferritinophagy); and iii) potential pharmacological modulators to enhance ER-phagy-mediated cytoprotection without inducing excessive ER degradation. Key ER-phagy receptors, mechanisms, experimental models and main outcomes in ARDS are summarized in Table IV.

Collectively, Tables I-IV summarize the molecular regulators, signaling pathways and experimental evidence that associate different autophagy subtypes with ARDS pathogenesis. Macroautophagy (Table I) exhibits clear context-dependent effects, exerting protective roles during the acute inflammatory phase while becoming potentially maladaptive when excessively or persistently activated. Ferritinophagy (Table II) has emerged as a key regulator of iron homeostasis, associating NCOA4-mediated ferritin degradation with ferroptotic cell death and lung injury, particularly in septic ARDS models. Mitophagy (Table III), primarily governed by the PINK1/Parkin axis and its upstream modulators, preserves mitochondrial integrity and limits inflammatory damage; however, the therapeutic efficacy of interventions targeting the PINK1/Parkin-mediated mitophagy pathway—that is, the effectiveness of modulating-mitophagy to preserve mitochondrial integrity and limit inflammatory damage likely depends on precise temporal and cell-type-specific regulation. ER-phagy (Table IV), through UPR-associated pathways and selective ER receptors, contributes to the maintenance of ER homeostasis, immune regulation and stress adaptation in ALI/ARDS.

Collectively, this evidence highlights both the shared and distinct mechanisms by which selective autophagy pathways influence inflammation, cell survival and tissue remodeling

Table IV. Roles and molecular mechanisms of ER-phagy in ARDS.

First author, year	Drug/molecule or receptor	ER-phagy state	Main molecular targets and pathways	Experimental model	Main conclusion	(Refs.)
Liu <i>et al.</i> , 2023	ER-phagy (general activation)	Activates	ER stress, UPR signaling and apoptosis	ALI/ARDS animal and cellular models (ARDS-specific)	Maintains ER homeostasis, reduces inflammation and cell death	(47)
Hübner <i>et al.</i> , 2020	FAM134B, RTN3L, SEC62 and ATL3	Activates	Selective ER fragment recognition and degradation	Various disease models including ALI-related studies (pulmonary relevant)	ER-phagy receptors represent potential therapeutic targets for ARDS	(48)

ER-phagy, ER-selective autophagy; FAM134B, family with sequence similarity 134 member B; RTN3L, reticulon 3 long isoform; SEC62, SEC62 preprotein translocation regulator; ATL3, atlastin GTPase 3; ER, endoplasmic reticulum; UPR, unfolded protein response; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

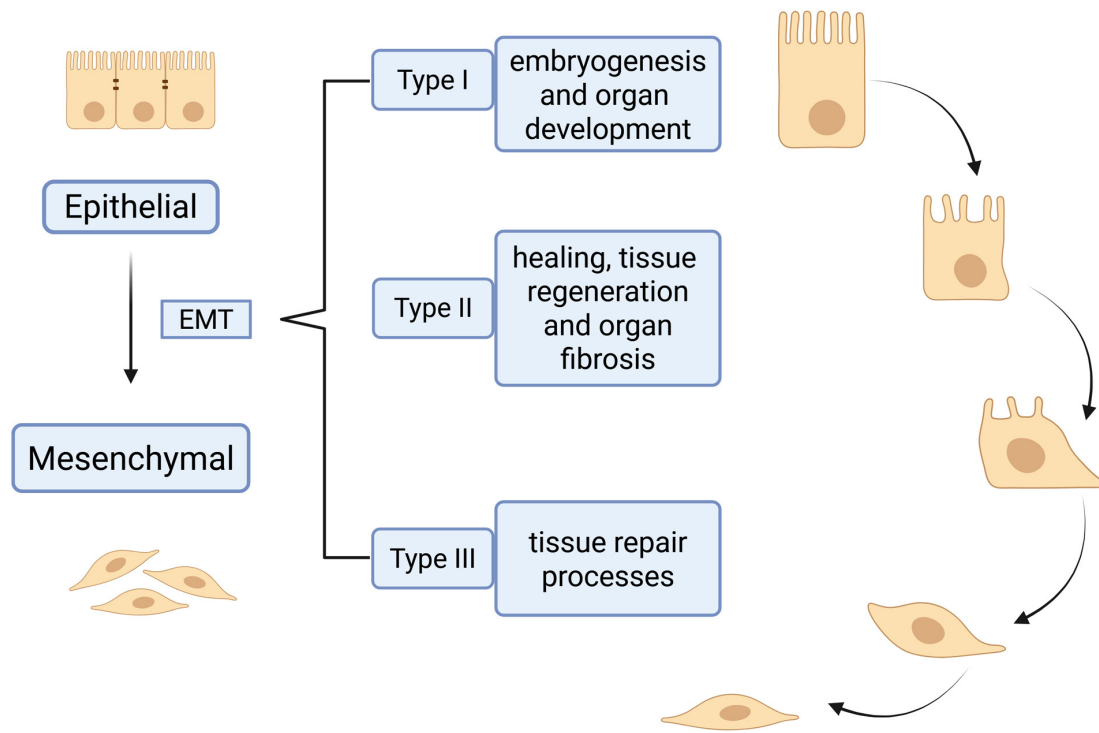


Figure 3. Classification of EMT and relevance to ARDS. Schematic depicting the conversion from epithelial to mesenchymal phenotypes and three EMT subtypes. Type I EMT: Occurs during embryogenesis and organ development. Epithelial cells gradually acquire mesenchymal traits (extrapolated evidence). Type II EMT: Associated with wound healing, tissue regeneration and organ fibrosis. Closely resembles EMT observed in ARDS, driven by profibrotic and inflammatory signaling, including TGF- β , WNT/ β -catenin and Notch pathways (ARDS-specific). Type III EMT: Implicated in cancer invasion and metastasis (extrapolated evidence). Arrows indicate phenotypic transitions. Dashed boxes highlight ARDS-relevant Type II EMT. Schematic emphasizes the context- and disease-specific nature of EMT in fibrotic lung remodeling. EMT, epithelial-mesenchymal transition; ARDS, acute respiratory distress syndrome.

in ARDS, underscoring the importance of coordinated and context-aware modulation of autophagy for therapeutic intervention.

4. EMT in ARDS pathogenesis

EMT and core mechanisms. EMT is a dynamic and reversible biological process in which epithelial cells progressively lose apical-basal polarity and intercellular junctions while acquiring mesenchymal characteristics, including enhanced migratory capacity and increased ECM production (55). EMT serves key roles in embryonic development, wound healing and tissue regeneration. However, persistent or dysregulated EMT contributes to pathological conditions such as organ fibrosis and cancer progression (56).

Notably, EMT is not restricted to epithelial cells of ectodermal origin. Endothelial cells can undergo a closely related process termed the EndMT, which has been increasingly implicated in vascular dysfunction and fibrotic remodeling. Within the context of lung injury and ARDS, both epithelial EMT and EndMT contribute to fibroblast accumulation and ECM deposition. For conceptual clarity and consistency, the present review uses the term ‘EMT’ as an umbrella concept, while explicitly specifying EndMT where endothelial-derived transitions are discussed.

At the molecular level, EMT is characterized by the coordinated downregulation of epithelial markers, such as E-cadherin and zonula occludens 1 and upregulation of mesenchymal markers, including α -smooth muscle actin, vimentin

and fibronectin (55-57). This phenotypic shift disrupts adherens and tight junctions, alters cytoskeletal organization and compromises epithelial barrier integrity, features highly relevant to ARDS pathophysiology (58-60).

Based on biological context, EMT is commonly classified into three subtypes (Fig. 3): i) Type I EMT during embryogenesis; ii) type II EMT associated with tissue repair and organ fibrosis; and iii) type III EMT involved in cancer invasion and metastasis (61). In ARDS and other fibrotic lung diseases, EMT most closely resembles type II EMT and is driven by profibrotic and inflammatory signaling pathways, including TGF- β , Sonic Hedgehog WNT/ β -catenin and Notch pathways (62). Fig. 3 highlights how epithelial cells transition to mesenchymal phenotypes, contributing to fibroproliferative remodeling. These pathways converge on EMT-associated transcription factors such as zinc-finger transcription factor SNAIL1 (Snail), Snail family transcriptional repressor 2 (SLUG) and zinc finger E-box-binding homeobox family members to initiate and sustain mesenchymal reprogramming (63). Aberrant or prolonged activation of these signaling networks promotes pathological fibrosis, highlighting EMT as a potential therapeutic target in fibrotic lung disease.

EMT contribution to ARDS progression. EMT has emerged as an important contributor to pulmonary fibrotic remodeling in a subset of ARDS survivors. In the injured lung, persistent epithelial damage, oxidative stress and profibrotic mediators, most prominently TGF- β 1, foster a microenvironment that favors partial or sustained EMT activation. While EMT is

well characterized in cancer biology, its extent, timing and functional relevance in ARDS-associated fibrosis remain incompletely defined (64-67).

Clinically, post-ARDS pulmonary fibrosis is associated with impaired lung compliance, prolonged ventilator dependence and increased long-term mortality. Histopathological analyses of fibrotic lung tissue from ARDS models and patients has revealed that epithelial cells express mesenchymal markers, supporting the involvement of EMT-related programs in fibrogenesis (5,16). Rather than representing a complete phenotypic conversion, EMT in ARDS is increasingly regarded as a partial or hybrid state, in which epithelial cells acquire mesenchymal features that promote fibroblast activation, ECM deposition and disruption of alveolar architecture (68-71).

Experimental intervention studies provide mechanistic evidence associating EMT with fibrotic outcomes in ARDS (65,72-74). In an LPS-induced ARDS model, treatment with the histone methyltransferase inhibitor 3-deazaneplanocin A was found to attenuate lung injury and fibrosis by suppressing EMT through inhibition of the TGF- β 1/Smad signaling pathway (75). Similarly, pirfenidone, a clinically approved antifibrotic agent, reduces fibrotic remodeling by inhibiting EndMT, highlighting the contribution of mesenchymal transition programs beyond epithelial cells in ARDS (76). Resveratrol has also been shown to suppress EMT-related marker expression by alleviating oxidative stress and downregulating TGF- β 1 signaling, further supporting EMT as a modifiable process in experimental ARDS (77).

At the molecular level, TGF- β 1 acts as a central driver of EMT by inducing phosphorylation of Smad2 and Smad3, which translocate to the nucleus and activate transcriptional programs favoring mesenchymal differentiation. By contrast, Smad7 functions as an endogenous inhibitory regulator that restrains excessive TGF- β signaling and limits fibrotic progression (78). The balance between these signaling components perhaps determines whether EMT contributes to adaptive repair or maladaptive fibrosis in ARDS. Despite growing experimental evidence, knowledge gaps still persist (65,73,74,79). The temporal dynamics of EMT activation during the acute, resolving and fibrotic phases of ARDS remain unclear, as does the relative contribution of different cell types, including alveolar epithelial cells, endothelial cells and fibroblasts, to EMT-driven remodeling. These uncertainties limit the translation of EMT-targeted strategies into clinical practice. Overall, EMT represents a key but context-dependent mechanism in ARDS-associated pulmonary fibrosis. Therapeutic modulation of EMT-related signaling pathways, particularly TGF- β -Smad signaling, holds promise but requires precise consideration of disease stage, cellular targets and interaction with parallel injury and repair pathways. Future studies integrating cell-type-specific approaches and longitudinal analyses are therefore key in clarifying the pathogenic vs. reparative roles of EMT in ARDS.

5. Interplay between autophagy and EMT

Evidence scope and interpretative framework. Mechanistic associations between autophagy and EMT discussed in the following section are derived from a combination of

ARDS/ALI models and extrapolative evidence from other disease contexts, including cancer, metabolic disorders and chronic fibrotic diseases. Where available, findings directly obtained from ARDS- or lung injury-relevant experimental systems are explicitly highlighted. By contrast, mechanistic insights originating from non-pulmonary or non-ARDS models are clearly identified as extrapolative and are discussed in light of their potential relevance and limitations for ARDS pathophysiology. This integrative approach was adopted as evidence associating specific autophagy subtypes with EMT in ARDS remains limited, yet shared stress-response pathways, such as oxidative stress, metabolic reprogramming, mitochondrial dysfunction, iron dysregulation and ER stress, providing a rational basis for cautious mechanistic inference. Throughout the following sections, emphasis is placed upon context-dependent determinants, including cell type, stage of injury and autophagy subtype, to avoid overgeneralization and frame testable hypotheses for future ARDS-focused studies.

Macroautophagy and EMT: Context-dependent regulatory roles. Macroautophagy is a key cellular process that influences EMT by regulating energy homeostasis, redox balance and selective protein turnover, all of which are important in EMT-associated phenotypic plasticity. Accumulating evidence has indicated that macroautophagy does not exert a uniform effect on EMT; instead, its impact is highly context-dependent, varying with cell type, metabolic state and disease stage (65,73,74,79).

Early mechanistic insights from liver-specific autophagy-deficient mice (Albumin-Cre; autophagy-related Gene 7^{fl/fl}) demonstrated that autophagy impairment is associated with downregulation of epithelial markers and upregulation of mesenchymal markers, suggesting that autophagy deficiency can facilitate EMT progression (80). One well-characterized mechanism underlying this effect is the selective autophagic degradation of the EMT-inducing transcription factor Snail through a p62/sequestosome 1 (SQSTM1)-dependent pathway (80-83). By limiting Snail accumulation, basal autophagy acts as a restraining force on EMT initiation.

In addition to selective protein degradation, core autophagy-related proteins such as LC3 and beclin-1 influence EMT by modulating cytoskeletal organization and the balance of epithelial and mesenchymal adhesion molecules, including E-cadherin and N-cadherin (84). These structural and signaling effects underscore a bidirectional relationship in which EMT-associated cytoskeletal remodeling and metabolic reprogramming can, in turn, feedback to regulate autophagic flux.

Notably, ARDS-relevant studies provide evidence that macroautophagy can suppress EMT under inflammatory and hypoxic conditions (64,83,85,86). In LPS-induced ARDS models, pharmacological activation of autophagy by inositol inhibits the hypoxia-inducible factor 1 α (HIF-1 α)/SLUG signaling axis, leading to reduced EMT marker expression and attenuation of pulmonary fibrosis (85). These findings support a protective role for macroautophagy in limiting maladaptive EMT during lung injury and repair.

Conversely, evidence from non-pulmonary disease models highlights the pro-EMT role of autophagy under

specific metabolic conditions (82,87-89). In cancer cells, autophagy-derived acetyl-CoA promotes acetylation and stabilization of Snail, thereby enhancing EMT through upregulation of mesenchymal markers such as vimentin and repression of epithelial markers including E-cadherin (87). This metabolic-epigenetic mechanism illustrates how sustained or excessive autophagy may facilitate EMT by fueling transcriptional programs that favor mesenchymal differentiation.

Collectively, these conflicting findings can be reconciled by a context-dependent model. In the early or acute phase of tissue injury, moderate autophagy may exert protective effects by degrading EMT drivers, limiting oxidative stress and preserving epithelial identity. By contrast, during prolonged stress, chronic inflammation or altered metabolic states, autophagy may support EMT progression by providing biosynthetic substrates and epigenetic regulators that reinforce mesenchymal programs. In addition, cell-type specificity, such as differences between epithelial cells, fibroblasts and immune cells, likely further determines the direction and magnitude of autophagy-EMT interactions.

From an ARDS perspective, these insights suggest that therapeutic modulation of macroautophagy must consider timing, intensity and cellular targets. Non-selective activation or inhibition of autophagy may yield divergent outcomes depending on disease stage and microenvironment. Therefore, future studies integrating temporal analysis, cell-specific genetic models and multi-omics approaches are required to delineate when macroautophagy restrains EMT and when it inadvertently promotes fibrotic remodeling. Such findings will be key in translating autophagy-EMT crosstalk into rational therapeutic strategies for ARDS. The available evidence supporting context-dependent roles of macroautophagy in EMT regulation, including ARDS/ALI-relevant and extrapolative studies, is summarized in Table V.

Mitophagy and EMT: Context-dependent crosstalk and mechanisms insights. Mitophagy, the selective autophagic elimination of damaged or dysfunctional mitochondria, has been increasingly recognized as a regulator of EMT through its control of mitochondrial quality, ROS generation and metabolic signaling (90-93). However, similar to macroautophagy, the impact of mitophagy on EMT is highly context-dependent and varies across cell types and pathological conditions.

Evidence from non-pulmonary disease models has illustrated that suppression of mitophagy can facilitate EMT. In endothelial cells infected with Kaposi's sarcoma-associated herpesvirus, activation of the mTOR pathway and its downstream effectors 4E binding protein 1 and ULK1 inhibits mitophagy, leading to mitochondrial dysfunction and induction of EMT programs (94). Similarly, in retinal pigment epithelial cells, oxidative stress-induced impairment of mitophagy has resulted in mitochondrial damage and elevated ROS production, which activated EMT signaling pathways and exacerbated epithelial dysfunction in age-related macular degeneration models (95). These studies support a model in which insufficient mitophagic clearance promotes EMT by amplifying mitochondrial stress signals.

By contrast, pulmonary-relevant models have suggested that excessive or sustained mitophagy may also contribute to EMT-associated pathology. In mice chronically exposed

Table V. Relationship between macroautophagy and EMT.

First author, year	Drug/molecule	Autophagy state	Molecular targets	Experimental model	Main conclusion	(Refs.)
Grassi <i>et al.</i> , 2015	Basal autophagy	Activates	p62/SQSTM1	Liver-specific autophagy-deficient mice (Alb-Cre; ATG7 ^{fl/fl})	Deficiency promotes EMT	(80)
Colella <i>et al.</i> , 2019	LC3 and beclin-1	Activates	Snail, N-cadherin and E-cadherin	<i>In vitro</i> alveolar epithelial cells (pulmonary relevant)	Modulates EMT	(84)
Liang <i>et al.</i> , 2022	Inositol	Activates	HIF-1 α /SLUG signaling pathway	LPS-induced alveolar epithelial cells and LPS-induced ARDS mouse model (ARDS-specific)	Inhibits EMT and alleviates pulmonary fibrosis	(85)
Han <i>et al.</i> , 2022	Autophagy-derived acetyl-CoA	Activates	Snail, vimentin and E-cadherin	KL cancer cells	Promotes EMT through Snail acetylation	(87)

Snail, zinc-finger transcription factor SNAIL1; HIF-1 α , hypoxia-inducible factor 1 α ; SLUG, Snail family transcriptional repressor 2; KL, KRAS-LKB1; EMT, epithelial-mesenchymal transition; LPS, lipopolysaccharide; ARDS, acute respiratory distress syndrome; SQSTM1, sequestosome 1; Alb-Cre, Albumin-Cre; ATG7, autophagy related 7.

to particulate matter 2.5, enhanced mitophagy, reflected by increased Parkin, SQSTM1/p62 and light chain (LC)3B-II/LC3B-I ratios, coincided with elevated TGF-β1 expression and upregulation of mesenchymal markers, thereby promoting pulmonary inflammation and fibrotic remodeling through EMT activation (10). Although not classical ARDS models, these findings are relevant to lung injury and fibrosis and suggest that prolonged mitophagy activation under persistent environmental stress may support EMT-driven pathological remodeling. Collectively, these seemingly contradictory observations can be interpreted as biphasic, context-dependent models of mitophagy-EMT crosstalk. During acute injury or transient stress, mitophagy is likely protective by preserving mitochondrial integrity, limiting ROS accumulation and preventing EMT initiation. Conversely, during chronic injury, sustained inflammation or repeated environmental insults and excessive or dysregulated mitophagy may facilitate EMT by reinforcing profibrotic signaling pathways such as TGF-β1, metabolic reprogramming and persistent cellular stress responses. The direction of this effect is further shaped by cell type (epithelial vs. endothelial), mitochondrial reserve capacity and disease stage. From an ARDS perspective, direct evidence to associate mitophagy with EMT remains limited and much of the current understanding is extrapolated from other pulmonary or non-pulmonary disease models (72,90,96,97). This highlights an important knowledge gap and underscores the need for ARDS-specific studies that interrogate mitophagy-EMT interactions in alveolar epithelial cells, endothelial cells and immune cells across different phases of lung injury and repair.

Future investigations should therefore focus on defining the spatiotemporal dynamics of mitophagy during EMT transitions in ARDS-relevant models. Integration of cell-specific genetic approaches, live-cell imaging of mitochondrial turnover and single-cell transcriptomic and metabolomic analyses will be key in clarifying when mitophagy restrains EMT and when it contributes to fibrotic progression. Such insights will be important in the rational design of mitophagy-targeted interventions aimed at limiting EMT-driven lung fibrosis in ARDS. Current evidence regarding mitophagy and EMT regulation, derived from ARDS-relevant models and extrapolative disease settings, is summarized in Table VI.

Ferritinophagy and EMT: Context-dependent regulation and translational implications. Ferritinophagy is a selective autophagic process that degrades ferritin to regulate intracellular iron availability and redox homeostasis. By releasing iron from ferritin complexes, ferritinophagy expands the labile iron pool, thereby enhancing ROS generation and lipid peroxidation. Given that oxidative stress is a key modulator of EMT, ferritinophagy has emerged as a potential upstream regulator of EMT through iron- and ROS-dependent signaling pathways (98).

The majority of mechanistic insights into ferritinophagy-EMT crosstalk are currently derived from cancer models rather than pulmonary or ARDS-specific systems. In colon carcinoma CT26 cells, the iron chelator 2,2'-dipyridone-2-thioacetate (DpdtP) activates NCOA4-dependent ferritinophagy, leading to increased intracellular ROS production and robust suppression of EMT marker expression (99).

Table VI. The relationship between mitophagy and EMT.

First author, year	Drug/molecule	Mitophagy state	Molecular targets	Experimental model	Main conclusion	(Refs.)
Santarelli <i>et al.</i> , 2020	KSHV	Inhibits	mTOR, 4EBP1 and ULK1	HUVEC cells and Kaposi's sarcoma model	Promotes EMT	(94)
Xu <i>et al.</i> , 2021	PM2.5	Activates	Parkin, SQSTM1/p62, LC3B-II/LC3B-I and TGF-β1	PM2.5-exposed mice	Promotes EMT and pulmonary fibrosis	(10)
Hytinen <i>et al.</i> , 2018	Oxidative stress	Inhibits	Mitochondria	RPE cells	Promotes EMT	(95)

EMT, epithelial-mesenchymal transition; PM, particulate matter; RPE, retinal pigment epithelial; 4EBP1, 4E binding protein 1; ULK1, unc-51 like autophagy activating kinase 1; Parkin, parkin RBR E3 ubiquitin protein ligase; SQSTM1, sequestosome 1; KSHV, Kaposi's sarcoma-associated herpesvirus.

Similar observations have been reported in a gastric cancer model, whereby dipyrilylhydrazone dithiocarbamate-induced ferritinophagy elevated ROS levels, activated p53 signaling and inhibited EMT progression in MGC-803 cells (100). In addition, DpdtbA enhances ferritinophagic flux and concomitantly activates the prolyl hydroxylase domain-containing protein 2/HIF-1 α axis together with p53, collectively restraining EMT in gastric carcinoma (11). These studies suggest that, under certain conditions, ferritinophagy-driven oxidative stress can function to alleviate EMT by engaging tumor suppressor pathways in highly proliferative or metabolically active cells. Beyond direct ROS signaling, ferritinophagy also intersects with EMT through ferroptosis-related mechanisms. For instance, D-camphor enhances cisplatin sensitivity by linking NCOA4-mediated ferritinophagy with ferroptosis and EMT suppression in cancer cells (101). However, extrapolation of these findings to ARDS must be approached with caution. For example, in a ventilator-induced lung injury, AMPK/ULK1-dependent NCOA4-mediated ferritinophagy was shown to drive ferroptosis and lung tissue damage, with inhibition of ferritinophagy attenuating iron overload, lipid peroxidation and pulmonary injury markers (102). Similarly, in a model of septic ARDS, melatonin was reported to ameliorate alveolar macrophage ferroptosis by inhibiting NCOA4-dependent ferritinophagy, leading to reduced iron-mediated ROS accumulation and improved lung histopathology (39). Collectively, in ARDS-relevant models, excessive or dysregulated ferritinophagy can exacerbate iron overload, ferroptotic cell death and inflammatory injury, which may indirectly facilitate EMT and fibrotic signaling through the iron-ROS-TGF- β axis. Therefore, a unifying framework could be proposed, whereby transient or moderate ferritinophagy may suppress EMT through ROS-mediated activation of p53 and related stress-response pathways, whereas sustained or excessive ferritinophagy in inflamed tissues may aggravate epithelial damage, reinforce profibrotic signaling and ultimately favor EMT-driven remodeling. Cell type-specific responses (epithelial cells vs. macrophages or fibroblasts) and differences between acute vs. chronic injury states are likely key determinants of these divergent outcomes.

From a translational perspective, targeting ferritinophagy is a two-sided therapeutic strategy. While inducing ferritinophagy may be beneficial for limiting EMT in cancer, inhibiting excessive ferritinophagy could be more appropriate in ARDS to prevent ferroptosis, epithelial barrier disruption and secondary fibrotic remodeling. Future ARDS-focused studies should therefore integrate iron metabolism profiling, EMT marker analysis and ferroptosis assessment in cell type-specific models to further determine these associations. Evidence implicating ferritinophagy in EMT regulation, primarily derived from extrapolative models with emerging relevance to ARDS, is summarized in Table VII.

ER-phagy and EMT: Context-dependent regulation and therapeutic potential. As a central organelle, the ER is responsible for protein folding, processing, calcium homeostasis and metabolic regulation. Disruptions in ER function can lead to the accumulation of misfolded proteins, causing ER stress that perturbs redox balance, energy metabolism, inflammation, differentiation and cell survival. To restore homeostasis,

cells deploy two primary quality control systems: i) The ubiquitin-proteasome pathway; and ii) selective autophagic clearance of the ER, termed ER-phagy (103). ER stress concurrently activates the UPR and ER-phagy and while the UPR primarily aims to reduce protein load and reestablish folding capacity, ER-phagy selectively degrades damaged or excess ER fragments through autophagosomes, facilitating ER recovery and preserving cellular homeostasis (104).

UPR activation is well regarded to promote EMT in cancer and fibrotic contexts through pathways including X-box binding protein 1 (XBP1), activating transcription factor 6 and eukaryotic translation initiation factor 2 α kinase 3, which converge on transcriptional programs that enhance mesenchymal marker expression and suppress epithelial traits (105-108). By contrast, the role of ER-phagy in modulating EMT has been emerging and appears largely protective. For example, in diabetic nephropathy, ER stress-induced ferroptosis through the XBP1-E3 ubiquitin-protein ligase Hrd-nuclear factor erythroid 2-related factor 2 axis drives EMT and tissue fibrosis (12). Conversely, activation of the ER-phagy receptor FAM134B in lung epithelial cells enhances selective ER clearance, reduces apoptosis, mitigates tissue injury and limits collagen deposition, collectively suppressing EMT and fibrotic remodeling in preclinical models (109). In LPS-induced ALI models, inhibition of ER stress with 4-phenylbutyric acid (4-PBA) attenuated pulmonary inflammation, lipid peroxidation and ferroptosis, suggesting that modulation of ER stress and related autophagic responses contributes to lung protection in ALI/ARDS contexts (110). Similarly, in hyperoxia-induced ALI, 4-PBA-mediated suppression of ER stress, alleviated pulmonary edema, reduced inflammatory responses and preserved barrier integrity, further implicating ER homeostasis as a determinant of injury severity in lung injury models (111). Additional ER-phagy receptors, such as RTN3L, SEC62 and ATL3, have been implicated in ER homeostasis and immune regulation, suggesting additional avenues for modulating EMT indirectly through ER quality control.

Notably, these observations indicate a context-dependent interplay between ER stress, UPR and ER-phagy, whereby, while persistent or excessive ER stress promotes EMT and tissue remodeling, ER-phagy functions as a protective mechanism that alleviates stress, preserves epithelial integrity and limits EMT progression. However, the precise molecular pathways that associate ER-phagy with EMT in ARDS or ALI remain incompletely defined and the majority of current evidence is extrapolated from cancer or renal disease models. Therefore, ARDS-specific investigations are required to further elucidate how ER-phagy modulates EMT in alveolar epithelial cells, endothelial cells and immune cell populations under inflammatory or fibrotic conditions. From a translational perspective, targeting ER-phagy offers a promising strategy to mitigate EMT-associated fibrosis and tissue remodeling. Potential approaches include pharmacological enhancement of ER-phagy receptors, modulation of UPR signaling to prevent maladaptive EMT and cell type-specific interventions that preserve ER homeostasis while minimizing systemic effects (112-114). Future studies should therefore integrate ER stress profiling, EMT marker assessment and functional outcomes in ARDS-relevant preclinical models to validate

Table VII. Relationship between ferritinophagy and EMT.

First author, year	Drug/molecule	Ferritinophagy state	Molecular targets	Experimental model	Main conclusion	(Refs.)
Sun <i>et al.</i> , 2019	DpdtpA	Activates	NCOA4/ferritin	CT26 colon carcinoma cells	Inhibits EMT	(99)
Feng <i>et al.</i> , 2020	DpdtC	Activates ferritinophagy	ROS/p53 pathway and ferritin	MGC-803 gastric cancer cells	Suppresses EMT	(100)
Guan <i>et al.</i> , 2021	DpdtbA	Activates	Ferritin, p53, PHD2 and HIF-1 α	SGC-7901 and MGC-803 gastric cancer cells	Inhibits EMT	(11)
Li <i>et al.</i> , 2022	D-Camphor	Activates	NCOA4 and EMT-related signaling	H460/CDDP xenograft tumor model	Inhibits EMT	(101)
Ou <i>et al.</i> , 2024	Mechanical ventilation (VILI)	Activates	AMPK/ULK1-NCOA4 pathway; ferroptosis	Ventilator-induced lung injury mouse model	Promotes ferroptosis and lung tissue injury, potentially facilitating EMT-associated remodeling	(102)
Xu <i>et al.</i> , 2024	Melatonin	Inhibits	NCOA4-dependent ferritin degradation; iron-ROS axis	Septic ARDS mouse model; alveolar macrophages	Alleviates ferroptosis and lung injury, indirectly limiting EMT-associated damage	(39)

EMT, epithelial-mesenchymal transition; ROS, reactive oxygen species; NCOA4, nuclear receptor coactivator 4; DpdtpA, 2,2'-dipyridone-2-thioacetate; DpdtC, dipyriddyldihydrozone dithiocarbamate; VILI, ventilator-induced lung injury; PHD2, prolyl hydroxylase domain-containing protein 2; HIF-1 α , hypoxia-inducible factor 1 α ; AMPK, AMP-activated protein kinase; ULK1, unc-51 like autophagy activating kinase 1.

Table VIII. Relationship between ER-phagy/ER stress and EMT.

First author, year	Drug/molecule	ER-phagy state	Molecular targets	Experimental model	Main conclusion	(Refs.)
Guo <i>et al.</i> , 2024	FAM134B	Activates	ER stress, FAM134B, apoptosis and collagen deposition	RLE-6TN alveolar epithelial cells; rat model	Inhibits EMT and fibrosis	(109)
Liu <i>et al.</i> , 2023	XBP1-HRD1-Nrf2	Activates	XBP1, HRD1 and Nrf2	Streptozotocin-induced DN mice and HK-2 cells	Promotes EMT	(12)
Wang <i>et al.</i> , 2024	4-PBA	Inhibits	ER stress, lipid peroxidation and ferroptosis	LPS-induced acute lung injury mouse model	Attenuates lung injury and limits EMT-associated remodeling	(110)
Pao <i>et al.</i> , 2021	4-PBA	Inhibits	ER stress, inflammation and barrier integrity	Hyperoxia-induced acute lung injury mouse model	Alleviates pulmonary injury and preserves epithelial integrity	(111)

EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; LPS, lipopolysaccharide; 4-PBA, 4-phenylbutyric acid; HRD1, E3 ubiquitin-protein ligase HRD1; XBP1, X-box binding protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; DN, diabetic nephropathy; FAM134B, family with sequence similarity 134 member B.

these strategies. Available studies examining the roles of ER-phagy and ER stress in EMT regulation, including extrapolative and limited ARDS-relevant evidence, are summarized in Table VIII.

The molecular mechanisms and functional outcomes of macroautophagy, mitophagy, ferritinophagy and ER-phagy in regulating EMT are summarized in Tables V-VIII. This evidence highlights that the effects of autophagy on EMT are highly context-dependent, varying by autophagy subtype, cellular environment and disease stage. For example, macroautophagy can either suppress or promote EMT depending on metabolic and epigenetic cues, whereas mitophagy shows bidirectional effects influenced by mitochondrial stress and ROS levels. Ferritinophagy predominantly inhibits EMT through ROS-mediated signaling and ferroptotic pathways, while ER-phagy typically mitigates EMT by alleviating ER stress and collagen deposition. Collectively, these findings support a model in which the interplay between autophagy subtype, temporal stage of injury and specific cell type determines whether EMT is restrained or facilitated, providing a framework for targeted therapeutic strategies in ARDS-associated fibrosis.

6. Discussion

Autophagy, both macroautophagy and selective subtypes including mitophagy, ferritinophagy and ER-phagy, serves a key role in regulating EMT and pulmonary fibrosis in ARDS. Macroautophagy maintains cellular homeostasis and protein turnover, modulating EMT through mechanisms such as p62-mediated Snail degradation, autophagy-derived acetyl-CoA and regulation of adhesion molecules. Mitophagy preserves mitochondrial quality, influencing EMT through ROS production, metabolic reprogramming and TGF- β 1 signaling. Ferritinophagy regulates intracellular iron and redox balance, with ROS-dependent modulation of EMT, while ER-phagy maintains ER homeostasis and alleviates stress-induced EMT. The effects of these autophagy pathways are highly context- and cell type-dependent, with outcomes influenced by injury stage, oxidative stress and local microenvironmental cues. Given the limited availability of ARDS-specific mechanistic studies, the present review incorporates evidence from other disease models, which should be interpreted with caution and validated in pulmonary systems. ARDS-specific mechanistic studies remain limited, yet direct evidence in ARDS/ALI models is strongest for macroautophagy (such as LPS-induced epithelial injury and fibrosis) and ER-phagy (such as FAM134B-mediated protection in lung epithelial cells). Mitophagy and ferritinophagy mechanisms are largely extrapolated from non-pulmonary models (such as cancer, retinal degeneration and nephropathy) but provide important mechanistic insights. This distinction is important in interpretation and translational planning, as extrapolated findings may not fully recapitulate pulmonary microenvironment or cell-type interactions in ARDS.

Despite growing mechanistic insights, a number of knowledge gaps remain. The majority of studies rely on single-cell or *in vitro* systems, limiting the understanding of multicellular interactions and spatiotemporal dynamics in the injured lung. The temporal regulation of autophagy-EMT interplay during

ARDS, from the acute injury phase to fibrosis resolution, remains poorly characterized. Furthermore, the contribution of endothelial cells, alveolar macrophages and fibroblasts in shaping EMT responses through selective autophagy is incompletely understood. Conflicting evidence, such as bidirectional effects of macroautophagy and mitophagy on EMT, underscores the need for context-specific and cell-specific analyses. Furthermore, existing animal models inadequately capture human ARDS heterogeneity, challenging translational relevance (115-118). To address these limitations, integrative, systems-level approaches are required. Multi-omics strategies (transcriptomics, proteomics and metabolomics), combined with live-cell imaging, may map autophagy-EMT dynamics in relevant cell types and disease phases. Well-characterized patient-derived samples, stratified by ARDS stage and etiology, are key in validating preclinical mechanisms and identifying biomarkers for clinical translation. Tables I-VIII summarize autophagy subtypes, molecular targets, experimental models and outcomes, providing a comprehensive reference for dissecting autophagy-EMT crosstalk in ARDS. The present study proposes a phase- and cell type-dependent model of autophagy-EMT regulation in ARDS: i) Early injury phase: Protective macroautophagy and ER-phagy in epithelial and endothelial cells limit EMT and fibrosis; ii) persistent or maladaptive phase: Excessive mitophagy or ferritinophagy in alveolar macrophages or epithelial cells may promote ROS accumulation and mesenchymal transition, exacerbating fibrosis; and iii) cell type specificity: Epithelial cells, endothelial cells and immune cells display distinct autophagy-EMT responses, suggesting targeted interventions could optimize therapeutic outcomes.

With regard to translational guidance, selective modulation of autophagy subtypes offers potential strategies to restrain EMT and fibrosis in ARDS: i) Macroautophagy: Moderate activation may preserve epithelial identity and limit EMT, with excessive activation in late injury perhaps enhancing pro-fibrotic signaling; ii) mitophagy: Fine-tuning in macrophages and epithelial cells may prevent ROS-driven EMT without impairing mitochondrial quality control; iii) ferritinophagy: Inhibition of excessive ferritinophagy could prevent ferroptosis and epithelial barrier disruption, whereas transient activation may have protective effects in other contexts; iv) ER-phagy: Pharmacological enhancement of ER-phagy receptors (such as FAM134B) can relieve ER stress, reduce apoptosis and mitigate EMT progression; and v) practical considerations: Timing, intensity and cell type specificity are key and off-target effects and systemic autophagy modulation must be carefully monitored. Biomarkers, such as LC3-II, NCOA4, ROS levels and EMT markers, are able to guide intervention assessment.

With regard to research priorities, in order to advance ARDS-targeted therapies, future studies should aim to focus on the following: i) ARDS-specific validation of selective autophagy-EMT interactions in epithelial, endothelial and immune cells; ii) temporal mapping of autophagy-EMT dynamics across acute injury, repair and fibrotic phases; iii) integration of multi-omics, live-cell imaging and spatial transcriptomics to capture cell-specific autophagy responses; iv) identification of reliable, cell-type-specific biomarkers for clinical translation; and v) testing targeted

interventions in well-characterized ARDS preclinical models and patient-derived samples.

In conclusion, autophagy-EMT crosstalk constitutes a key determinant of ARDS progression and fibrosis. The present review summarized preclinical evidence across macroautophagy, selective autophagy subtypes and EMT mechanisms, highlighting context-, phase- and cell-specific effects. Understanding these regulatory networks will inform the rational design of autophagy-targeted therapies to mitigate pulmonary fibrosis, preserve lung function and improve outcomes in patients with ARDS. Focused translational research is needed to bridge mechanistic insights and clinical application.

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Authors' contributions

YZ wrote, reviewed and edited the original draft of the manuscript and contributed towards visualization. HH wrote, reviewed and edited the manuscript and conducted the literature search and screening. CD and QG were involved in visualization. JT and YY conducted the literature search and screening. ZG contributed towards the conceptualization and supervision of the present study. RZ contributed towards conceptualization, supervision and project administration. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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