Review

Targeting Mitochondrial Dynamics and Dysfunction in the Spectrum of Lung Diseases

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Posted Date: 5 August 2025

doi: 10.20944/preprints202508.0344.v1

Keywords: mitochondria; reactive oxygen species (ROS); pulmonary dysfunction; oxidative stress; asthma; COPD

 doi:10.20944/preprints202508.0344.v1

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Targeting Mitochondrial Dynamics and Dysfunction in the Spectrum of Lung Diseases

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Abstract

Mitochondrial structural and functional alterations have been linked to pathogenesis and disease progression across a spectrum of chronic and acute lung diseases. With substantial and diverse energy requirements, the metabolically active lungs support essential functions such as gas exchange, mucociliary clearance, and immune defense. This review focuses on the critical role of mitochondrial mechanisms and their subsequent dysfunction in the pathogenesis and progression of several debilitating lung pathologies. Specifically, we will explore how changes in mitochondrial dynamics (fusion and fission), bioenergetics, quality control mechanisms such as mitophagy, and the production of reactive oxygen species (ROS) contribute to the cellular and molecular foundations of various lung diseases. These pathologies include asthma, which is often manageable; COPD and idiopathic pulmonary fibrosis (IPF), which cause progressive decline; and acute respiratory distress syndrome (ARDS) and lung cancer, which can be immediately life-threatening. This review highlights the growing understanding of mitochondrial dysfunction as a central factor in the development and progression of lung diseases. It focuses on how disruptions in mitochondrial homeostasis contribute to disease pathogenesis and the potential implications of mitochondria-targeted therapeutic approaches to improve patient outcomes.

Keywords: mitochondria; reactive oxygen species (ROS); pulmonary dysfunction; oxidative stress; asthma; COPD

1. Introduction

The lungs are metabolically active organs with substantial and diverse energy demands to sustain critical functions such as gas exchange, mucociliary clearance, immune surveillance and lipid metabolism [1–3]. Mitochondria serve as the primary ATP source for these processes, particularly in energy-intensive cell types. For instance, alveolar type II (ATII) cells rely on oxidative phosphorylation (OXPHOS) to produce lung surfactant, a lipid-protein complex essential for reducing alveolar surface tension. Lower surface tension decreases the work required to inflate the lungs, improving pulmonary compliance [4]. Ciliated epithelial cells require ATP to power ciliary beating for mucociliary clearance, a frontline defense against pathogens [5]. Additionally, immune cells (e.g., macrophages) depend on mitochondrial metabolism to fuel phagocytosis and cytokine production during inflammation, while endothelial cells utilize mitochondrial ATP to maintain vascular integrity and regulate pulmonary blood flow [3,5]. These diverse metabolic requirements reflect adaptations to the lung's unique microenvironment, where oxygen tension fluctuates dynamically. ATII cells maintain bioenergetic homeostasis even under hypoxia by balancing glycolysis and OXPHOS, while immune cells rapidly upregulate glycolysis during activation ("Warburg effect") [6–8]. This adaptability underscores the critical role of mitochondria in

 doi:10.20944/preprints202508.0344.v1

maintaining lung function across varying physiological conditions. The goal of this review is to provide a timely and comprehensive synthesis of recent advances in understanding how mitochondrial dysfunction contributes to the pathogenesis of lung diseases. By summarizing the latest research, this review addresses the urgent need for up-to-date guidance in a landscape where both the complexity of mitochondrial biology and the range of potential interventions are expanding quickly. In this review, we summarize recent work (Jan 2023 to June 2025) examining how disruptions in mitochondrial dynamics (fusion and fission), bioenergetics, quality control (mitophagy), and reactive oxygen species (ROS) production contribute to cellular and molecular abnormalities underlying conditions such as asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), acute respiratory distress syndrome (ARDS), and lung cancer.

2. Methods

This literature review aimed to synthesize recent research on mitochondrial dysfunction across five major lung diseases: asthma, COPD, IPF, ARDS, and lung cancer. The review focused on studies published between **January 2023 and June 2025**.

2.1. Search Strategy

A comprehensive search was conducted using Google Scholar. Search terms were structured to capture both general mitochondrial dysfunction and disease-specific mechanisms. Boolean operators were used to combine keywords and refine results. Table 1 outlines the search strategy used for each disease.

Table 1. Summary of Search Strategy and Article Selection.

Disease	Keyword Used	Initial Hits	Screened[1]
Asthma	"mitochondrial dysfunction" AND "asthma"	903	90
COPD	"mitochondria" AND "COPD" OR "chronic obstructive pulmonary disorder"	503	65
IPF	"mitochondrial ROS" AND "IPF" OR "idiopathic pulmonary fibrosis"	125	43
ARDS	"mitochondria" AND "ARDS" OR "acute respiratory distress syndrome"	253	58
Lung cancer	"mitochondrial dysfunction" AND "lung cancer" OR "small cell lung cancer" OR "NSCLC"	2,208	101

[1] "Screened" includes full text reviews.

2.2. Inclusion and Exclusion Criteria

Studies were included based on the following criteria:

- Peer-reviewed original research, reviews, or meta-analyses.
- Published between January 2023 and June 2025.
- Written in English.
- Focused on mitochondrial structure, function, or signaling in relation to one of the target lung diseases.

Studies were excluded if they:

- Were published before January 2023.
- Did not include specific lung pathology context.
- Were preprints, editorials, or non-peer-reviewed sources.
- Focused solely on unrelated organ systems or generalized mitochondrial mechanisms without pulmonary context.

 doi:10.20944/preprints202508.0344.v1

2.3. Screening and Data Extraction

Initial screening was based on titles and abstracts, followed by full-text reviews. For each eligible study, data were extracted on:

- Type of study (basic, clinical, or translational)
- Mitochondrial parameters examined (e.g., ROS production, ATP levels, mitophagy, biogenesis)
- Key findings related to disease progression, diagnosis, or therapeutic targeting
- Studies were grouped by disease category to allow cross-comparison of mitochondrial dysfunction patterns.

2.4. Limitations

The use of Google Scholar, while broad in scope, may have excluded certain high-impact studies indexed exclusively in databases like PubMed or Web of Science. To mitigate this, rigorous manual screening and cross-checking of references were performed to ensure coverage and relevance. The selection process targeted peer-reviewed primary research and comprehensive review articles, as detailed in Table 1. Only articles in English were considered.

3. Results

3.1. Mitochondrial Dysfunction: A Multidimensional Pathology

Mitochondrial dysfunction extends beyond reduced ATP production, encompassing interrelated disruptions. Oxidative stress is a key factor, where excessive mitochondrial ROS (mtROS) damage lipids, proteins, and mtDNA, exacerbating inflammation and cellular injury [9–11]. In COPD, excess mtROS amplify NLRP3 inflammasome activation, leading to the release of the pro-inflammatory cytokine IL-1β, a key driver of lung inflammation [12]. Additionally, impaired mitochondrial biogenesis (via PGC-1α/NRF-1 pathways) and unbalanced fusion/fission (regulated by MFN1/2, DRP1) disrupt network integrity, leading to fragmented or hyperfused organelles [13,14]. In pulmonary fibrosis, excessive fission promotes fibroblast proliferation via mtROS-TGF-β signaling [15]. Furthermore, collapse of the mitochondrial membrane potential triggers the opening of mitochondrial permeability transition pore (MPTP), precipitating apoptosis or necrosis in alveolar cells [16]. Lastly, mtDNA mutations impair electron transport chain (ETC) function, perpetuating metabolic inefficiency and inflammation [17]. These dysfunctions converge to impair cellular homeostasis, exacerbate oxidative stress, and promote pathological processes such as apoptosis, senescence, and pro-fibrotic signaling. The interplay between these mechanisms underscores the complexity of mitochondrial dysfunction in lung diseases.

3.2. Clinical Relevance: Targeting Mitochondria in Lung Disease

Mitochondrial dysfunction plays a central role in the pathogenesis of several lung pathologies. Therapeutic strategies aimed at restoring mitochondrial homeostasis hold significant promise for improving patient outcomes. Here, we review the evidence for the role of mitochondrial dysfunction in the pathogenesis of asthma, COPD, pulmonary fibrosis, ARDS and lung cancer. In asthma, allergen-induced mtROS activates Th2 inflammation, while mitochondrial antioxidants such as superoxide dismutase (SOD2) and its mimetics have been shown to reduce airway hyperreactivity [18,19]. Pulmonary fibrosis involves dysregulated mitophagy—a key mechanism for removing damaged mitochondria and fission driving fibroblast activation; fission inhibitors (e.g., Mdivi-1) show therapeutic potential [20]. ARDS is marked by mitochondrial damage in endothelial cells, exacerbating vascular leakage [21]. While there is no effective treatment for ARDS, urolithin A, a mitophagy enhancer with antioxidant properties, has been shown to reduce oxidative stress linked to ARDS [22]. Lastly, lung cancer cells exhibit a remarkable metabolic plasticity, often undergoing mitochondrial reprogramming even in normoxic conditions. This metabolic rewiring provides these

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rapidly proliferating cells with a bioenergetic advantage, enabling the generation of essential biosynthetic precursors and ATP to fuel their aggressive growth [8].

Therapeutic implications include mitochondrial-targeted antioxidants (MitoQ), ETC modulators, and regulators of dynamics (e.g., DRP1 inhibitors) [23,24]. Thus, by addressing mitochondrial dysfunction, these strategies aim to mitigate disease progression and enhance lung resilience.

3.2.1. Asthma

Asthma is a chronic inflammatory disease of the airways where mitochondrial dysfunction has emerged as a key contributor to airway inflammation [25]. Mitochondria actively contribute to the production of inflammatory mediators such as IL-4, IL-5 and leukotrienes, which drive the Th2 immune response characteristic of asthma [26,27]. Increased ROS production by dysfunctional mitochondria amplifies oxidative stress in airway epithelial cells, further promoting inflammation and tissue damage.

Exercise-induced bronchoconstriction (EIB), a common feature in asthma, may also be linked to mitochondrial dysfunction. During physical activity, increased metabolic demands can overwhelm dysfunctional mitochondria, leading to excessive ROS production and exacerbation of airway constriction [28]. This connection highlights the need for further research into the role of mitochondria in EIB.

Therapeutic strategies targeting mitochondrial dysfunction in asthma include the use of antioxidants to reduce oxidative stress and agents that modulate mitochondrial dynamics to restore cellular homeostasis. These approaches could potentially alleviate airway inflammation and improve clinical outcomes.

3.2.2. Chronic Obstructive Pulmonary Disease (COPD)

COPD is a progressive respiratory disease characterized by chronic bronchitis and emphysema, both of which are closely linked to mitochondrial dysfunction. Oxidative stress and the resulting mitochondrial damage play a central role in the pathogenesis of COPD. This damage manifests as mitochondrial swelling, loss of cristae, and impaired electron transport chain function. Together, these changes reduce ATP production and exacerbate cellular injury [29–31]. Cigarette smoke exposure further worsens mitochondrial dysfunction in COPD. Prolonged exposure to cigarette smoke disrupts mitochondrial function, leading to excessive production of ROS. The resulting ROS directly damages mtDNA and proteins, further increasing ROS levels and creating a vicious cycle of oxidative stress and mitochondrial injury [32,33].

Given the central role of mitochondria in COPD pathogenesis, mitochondrial-targeted therapies hold promise. Antioxidants such as MitoQ and SkQ1 have shown potential in reducing oxidative damage and improving mitochondrial function in preclinical models [23,34]. Additionally, therapies aimed at enhancing mitophagy and promoting mitochondrial biogenesis could mitigate disease progression by restoring mitochondrial homeostasis.

3.2.3. Pulmonary Fibrosis

Pulmonary fibrosis is characterized by excessive extracellular matrix (ECM) deposition and fibroblast activation, processes that are closely linked to mitochondrial dysfunction. Dysregulated mitochondrial dynamics, including increased fission mediated by dynamin-related protein 1 (DRP1), contribute to fibroblast activation and proliferation [24,35,36]. Additionally, oxidative stress from elevated mtROS levels promotes ECM deposition through TGF-β signaling pathways [37].

Mitochondrial dysfunction is also implicated in epithelial-mesenchymal transition (EMT), a process where epithelial cells lose their characteristics and acquire a mesenchymal phenotype, contributing to fibrosis [38–40]. Impaired mitophagy further exacerbates mitochondrial dysfunction

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in fibrotic lungs. Autophagy plays a dual role in pulmonary fibrosis by maintaining mitochondrial quality control while also influencing fibroblast survival under stress conditions.

Emerging therapies targeting mitochondrial pathways include DRP1 inhibitors such as Mdivi-1 and agents that enhance mitophagy or reduce mtROS levels [20]. These interventions hold promise for mitigating fibrosis progression by restoring mitochondrial homeostasis.

3.2.4. Acute Respiratory Distress Syndrome (ARDS)

ARDS is a severe inflammatory condition often triggered by sepsis or ventilator-induced lung injury (VILI), where mitochondrial dysfunction plays a pivotal role in pathogenesis [41]. In ARDS, excessive inflammation leads to oxidative stress, which damages mitochondria in alveolar epithelial cells and endothelial cells. This results in impaired ATP production, loss of membrane potential, and increased mtROS generation, further amplifying inflammation [42,43].

Sepsis-induced ARDS is particularly associated with widespread mitochondrial damage due to systemic inflammation. Similarly, VILI exacerbates oxidative stress in lung tissues, leading to endothelial barrier disruption and alveolar flooding [44]. Mitochondrial dysfunction contributes to these processes by promoting apoptosis and necrosis of lung cells. Therefore, therapeutic interventions aimed at correcting mitochondrial imbalances and damage present a therapeutic strategy for sepsis-induced ARDS.

3.2.5. Lung Cancer

Mitochondrial dysfunction is intricately linked to lung cancer pathogenesis through its roles in tumorigenesis, metastasis, and chemoresistance [45–47]. Tumor cells often exhibit reprogrammed metabolism characterized by increased glycolysis (Warburg effect) alongside functional ETC activity to support rapid proliferation. This metabolic reprogramming is facilitated by alterations in mitochondrial dynamics and biogenesis.

Mitochondrial dysfunction also promotes metastasis by enhancing cellular motility through ROS-mediated signaling pathways [48]. Furthermore, mutations in mtDNA can confer resistance to chemotherapy by altering apoptotic pathways or increasing drug efflux mechanisms [49,50].

Strategies targeting mitochondrial metabolism present promising therapeutic opportunities in lung cancer. Agents like ETC inhibitors or modulators of mitochondrial dynamics could selectively disrupt tumor cell energy production while minimizing harm to healthy cells. Furthermore, integrating these approaches with current treatments may combat chemoresistance and enhance patient survival.

4. Discussion

This review highlights the central role of mitochondria in the maintenance of lung health and the pathogenesis of diverse pulmonary diseases. The synthesis of recent literature underscores that mitochondrial dysfunction is not a consequence but a driver of key pathological processes in asthma, COPD, IPF, ARDS, and lung cancer. It is evident that disruptions in mitochondrial dynamics, bioenergetics, ROS homeostasis, and quality control mechanisms produce a cascade of cellular and tissue injuries, ultimately contributing to disease initiation and progression.

4.1. Integration of Key Findings

Across diseases, a recurring theme is the convergence of oxidative stress, defective mitophagy, and altered mitochondrial dynamics in perpetuating inflammation, apoptosis, and fibrogenesis. For example, the role of mitochondrial ROS as both a signaling molecule and a source of oxidative damage is well demonstrated in asthma and COPD, linking environmental insults such as allergens or cigarette smoke to cellular dysfunction. In pulmonary fibrosis and ARDS, the literature shows that excessive mitochondrial fission and impaired mitophagy foster pro-fibrotic and pro-inflammatory

 doi:10.20944/preprints202508.0344.v1

responses, while in lung cancer, mitochondrial reprogramming enables tumor cells to meet the energy and biosynthetic demands of uncontrolled proliferation.

Importantly, the reviewed studies point to cell type- and microenvironment-specific aspects of mitochondrial pathology—highlighting, for example, unique adaptations in ATII cells to hypoxia, or the metabolic plasticity of cancer cells. Such diversity reflects the complexity of pulmonary biology and the need for tailored therapeutic interventions.

4.2. Therapeutic Implications

The emerging therapeutic landscape for targeting mitochondrial dysfunction is promising. Preclinical investigations of antioxidants (such as MitoQ or SOD2 mimetics), mitochondrial fission inhibitors (like Mdivi-1), and mitophagy enhancers (e.g., urolithin A) demonstrate efficacy in restoring mitochondrial and cellular function in model systems. Additionally, modulating mitochondrial metabolism represents a novel approach in lung oncology, potentially overcoming chemoresistance by selectively compromising the bioenergetic flexibility of tumor cells.

However, translation from bench to bedside remains at an early stage. Most candidate therapies are in preclinical or early-phase clinical development, and their long-term efficacy and safety profiles require rigorous evaluation. Furthermore, given the heterogeneity of mitochondrial dysfunction across diseases and even among individual patients, therapies will likely need to be personalized, possibly through the use of biomarkers indicating specific mitochondrial defects.

4.3. Limitations and Future Directions

While this review provides a comprehensive snapshot of recent advances, it is not without limitations. The reliance on Google Scholar as the primary search engine may have introduced publication bias or failed to capture literature indexed exclusively in specialized biomedical databases. Additionally, restricting inclusion to English-language reports may have omitted relevant findings from non-English sources. The rapidly evolving nature of mitochondrial biology means that some mechanistic insights or therapeutic avenues may yet emerge beyond this review's temporal scope.

Future research should address several key gaps:

- Elucidating the interplay between mitochondrial dysfunction and genetic/epigenetic factors predisposing individuals to lung disease.
- Developing sensitive, clinically applicable biomarkers for mitochondrial dysfunction to aid diagnosis and guide therapy.
- Advancing clinical trials for mitochondria-targeted interventions across different lung diseases.
- Exploring combinatorial therapies that address mitochondrial dysfunction in conjunction with established anti-inflammatory, anti-fibrotic, or anti-neoplastic drugs.

4.4. Broader Significance

The findings summarized here suggest that a mitochondrial perspective is essential for a nuanced understanding of lung disease mechanisms. As mitochondria are central to both cellular energy provision and stress responses, their dysfunction represents a unifying vulnerability across otherwise heterogeneous lung pathologies. Optimizing mitochondrial health thus holds the promise not only of disease attenuation, but possibly of disease prevention and improved resilience to environmental challenges.

5. Conclusions

Recent research reaffirms that targeting mitochondrial dysfunction offers a unifying and compelling approach to combating a broad spectrum of lung diseases. Continued cross-disciplinary efforts are needed to translate these insights into effective clinical interventions and to fully realize the potential of mitochondrial medicine in respiratory health.

 doi:10.20944/preprints202508.0344.v1

Author Contributions: F.C.G.; Conceptualization, project administration, methodology, original draft preparation, writing—review and editing. A.J.B.; data curation. A.J.S, S.C.G.; review and editing. N.A.; editing, revision. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable- no new data were created.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ROS	Reactive oxygen species
COPD	Chronic obstructive pulmonary disorder
IPF	Idiopathic pulmonary fibrosis
ARDS	Acute respiratory distress syndrome
ATII	Alveolar type II
OXPHOS	Oxidative phosphorylation
ATP	Adenosine triphosphate
mtROS	Mitochondrial reactive oxygen species
mtDNA	Mitochondrial deoxyribonucleic acid
MPTP	Mitochondrial permeability transition pore
ETC	Electron transport chain
SOD2	Super oxidase dismutase 2
EIB	Exercise-induced bronchoconstriction
ECM	Extracellular matrix
EMT	Epithelial mesenchymal transition
VILI	Ventilator-induced lung injury

References

1. Rhoades RA. Influence of starvation on the lung: effect on glucose and palmitate utilization. J Appl Physiol. 1975 Mar;38(3):513–6.
2. Holt PG, Strickland DH, Wikström ME, Jahnsen FL. Regulation of immunological homeostasis in the respiratory tract. Nat Rev Immunol. 2008 Feb;8(2):142–52.
3. Alvarado A, Arce I. Metabolic Functions of the Lung, Disorders and Associated Pathologies. J Clin Med Res. 2016 Oct;8(10):689–700.
4. Liu G, Summer R. Cellular Metabolism in Lung Health and Disease. Annu Rev Physiol. 2019 Feb 10;81:403–28.
5. Morgan TE. Pulmonary surfactant. N Engl J Med. 1971 May 27;284(21):1185–93.
6. Villar PS, Vergara C, Bacigalupo J. Energy sources that fuel metabolic processes in protruding finger-like organelles. FEBS J. 2021 June;288(12):3799–812.
7. Liberti MV, Locasale JW. The Warburg Effect: How Does it Benefit Cancer Cells? Trends Biochem Sci. 2016 Mar;41(3):211–8.
8. Vanhove K, Graulus GJ, Mesotten L, Thomeer M, Derveaux E, Noben JP, et al. The Metabolic Landscape of Lung Cancer: New Insights in a Disturbed Glucose Metabolism. Front Oncol. 2019 Nov 15;9:1215.
9. Jiang JJ, Zhang GF, Zheng JY, Sun JH, Ding SB. Targeting Mitochondrial ROS-Mediated Ferroptosis by Quercetin Alleviates High-Fat Diet-Induced Hepatic Lipotoxicity. Front Pharmacol. 2022;13:876550.
10. Rhoads DM, Umbach AL, Subbaiah CC, Siedow JN. Mitochondrial reactive oxygen species. Contribution to oxidative stress and interorganellar signaling. Plant Physiol. 2006 June;141(2):357–66.

 doi:10.20944/preprints202508.0344.v1

11. Nissanka N, Moraes CT. Mitochondrial DNA damage and reactive oxygen species in neurodegenerative disease. FEBS Lett. 2018 Mar;592(5):728–42.
12. Trachalaki A, Tsitoura E, Mastrodimou S, Invernizzi R, Vasarmidi E, Bibaki E, et al. Enhanced IL-1β Release Following NLRP3 and AIM2 Inflammasome Stimulation Is Linked to mtROS in Airway Macrophages in Pulmonary Fibrosis. Front Immunol. 2021;12:661811.
13. Abu Shelbayeh O, Arroum T, Morris S, Busch KB. PGC-1α Is a Master Regulator of Mitochondrial Lifecycle and ROS Stress Response. Antioxidants (Basel). 2023 May 10;12(5):1075.
14. Adebayo M, Singh S, Singh AP, Dasgupta S. Mitochondrial Fusion and Fission: The fine-tune balance for cellular homeostasis. FASEB J. 2021 June;35(6):e21620.
15. O'Leary EM, Tian Y, Nigdelioglu R, Witt LJ, Cetin-Atalay R, Meliton AY, et al. TGF-β Promotes Metabolic Reprogramming in Lung Fibroblasts via mTORC1-dependent ATF4 Activation. Am J Respir Cell Mol Biol. 2020 Nov;63(5):601–12.
16. Bernardi P, Gerle C, Halestrap AP, Jonas EA, Karch J, Mnatsakanyan N, et al. Identity, structure, and function of the mitochondrial permeability transition pore: controversies, consensus, recent advances, and future directions. Cell Death Differ. 2023 Aug;30(8):1869–85.
17. Harada K, Yahata T, Onizuka M, Ishii T, Aziz Ibrahim A, Kikkawa E, et al. Mitochondrial Electron Transport Chain Complex II Dysfunction Causes Premature Aging of Hematopoietic Stem Cells. Stem Cells. 2023 Jan 1;41(1):39–49.
18. Choi G, Ju HY, Bok J, Choi J, Shin JW, Oh H, et al. NRF2 is a spatiotemporal metabolic hub essential for the polyfunctionality of Th2 cells. Proceedings of the National Academy of Sciences. 2024 July 9;121(28):e2319994121.
19. Tu W, Xiao X, Lu J, Liu X, Wang E, Yuan R, et al. Vanadium exposure exacerbates allergic airway inflammation and remodeling through triggering reactive oxidative stress. Front Immunol [Internet]. 2023 Jan 11 [cited 2025 July 23];13. Available from: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2022.1099509/full
20. Ahn SI, Choi SK, Kim MJ, Wie J, You JS. Mdivi-1: Effective but complex mitochondrial fission inhibitor. Biochemical and Biophysical Research Communications. 2024 May 28;710:149886.
21. Wang J, Meng S, Chen Y, Wang H, Hu W, Liu S, et al. MSC-mediated mitochondrial transfer promotes metabolic reprograming in endothelial cells and vascular regeneration in ARDS. Redox Report. 2025 Dec 31;30(1):2474897.
22. Jiao P, Wang Y, Ren G, Chu D, Li Y, Yang Y, et al. Urolithin A exerts a protective effect on lipopolysaccharide-induced acute lung injury by regulating HMGB1-mediated MAPK and NF-κB signaling pathways. Naunyn-Schmiedeberg's Arch Pharmacol. 2024 Aug 1;397(8):5765–77.
23. Rondeau JD, Lipari S, Mathieu B, Beckers C, Van de Velde JA, Mignion L, et al. Mitochondria-targeted antioxidant MitoQ radiosensitizes tumors by decreasing mitochondrial oxygen consumption. Cell Death Discov. 2024 Dec 27;10(1):514.
24. Targeting DNM1L/DRP1-FIS1 axis inhibits high-grade glioma progression by impeding mitochondrial respiratory cristae remodeling | Journal of Experimental & Clinical Cancer Research [Internet]. [cited 2025 July 23]. Available from: https://link.springer.com/article/10.1186/s13046-024-03194-6
25. Lin L, Liao Z hua, Li C qian. Insight into the role of mitochondrion-related gene anchor signature in mitochondrial dysfunction of neutrophilic asthma. Journal of Asthma. 2024 Sept 1;61(9):912–29.
26. Wang J, Zhang X, Zhang L, Liu Y, Wang G, Zhang HP, et al. Age-Related Clinical Characteristics, Inflammatory Features, Phenotypes, and Treatment Response in Asthma. The Journal of Allergy and Clinical Immunology: In Practice. 2023 Jan 1;11(1):210-219.e3.
27. Qiu C, Feng D. Efficacy and anti-inflammatory analysis of glucocorticoid, antihistamine and leukotriene receptor antagonist in the treatment of allergic rhinitis. World J Clin Cases. 2023 Oct 6;11(28):6725–32.
28. Lingitz MT, Kühtreiber H, Auer L, Mildner M, Krenn CG, Aigner C, et al. Circulating Antimicrobial Peptides as Biomarkers of Inflammation and Airway Dysfunction After Marathon Running. Biology. 2025 July;14(7):825.
29. Activation of Pink1/Parkin-mediated mitochondrial autophagy alleviates exertional heat stroke-induced acute lung injury in rats - Jiaxing Wang, Zhengzhong Sun, Liya Jiang, Lyv Xuan, Yunya Ma, Jiao Wang,

 doi:10.20944/preprints202508.0344.v1

Yan Gu, Yuxiang Zhang, 2024 [Internet]. [cited 2025 July 23]. Available from: https://journals.sagepub.com/doi/full/10.3233/CH-242100

30. Wu Z, Bezwada D, Cai F, Harris RC, Ko B, Sondhi V, et al. Electron transport chain inhibition increases cellular dependence on purine transport and salvage. Cell Metabolism. 2024 July 2;36(7):1504-1520.e9.
31. Clobetasol propionate, a Nrf-2 inhibitor, sensitizes human lung cancer cells to radiation-induced killing via mitochondrial ROS-dependent ferroptosis | Acta Pharmacologica Sinica [Internet]. [cited 2025 July 23]. Available from: https://www.nature.com/articles/s41401-024-01233-8
32. Saha P, Jain S, Mukherjee I, Panda SR, Zeki AA, Naidu VGM, et al. The effects of dual IQOS and cigarette smoke exposure on airway epithelial cells: implications for lung health and respiratory disease pathogenesis. ERJ Open Research [Internet]. 2023 May 30 [cited 2025 July 23];9(3). Available from: https://publications.ersnet.org/content/erjor/9/3/00558-2022
33. Tissue-specific mitochondrial toxicity of cigarette smoke concentrate: consequence to oxidative phosphorylation | American Journal of Physiology-Heart and Circulatory Physiology | American Physiological Society [Internet]. [cited 2025 July 23]. Available from: https://journals.physiology.org/doi/full/10.1152/ajpheart.00199.2023
34. Chen Y, Guo X, Zeng Y, Mo X, Hong S, He H, et al. Oxidative stress induces mitochondrial iron overload and ferroptotic cell death. Sci Rep. 2023 Sept 19;13(1):15515.
35. STAT3 phosphorylation at Tyr705 affects DRP1 (dynamin-related protein 1) controlled-mitochondrial fission during the development of apoptotic-resistance in pulmonary arterial endothelial cells | Genes & Genomics [Internet]. [cited 2025 July 23]. Available from: https://link.springer.com/article/10.1007/s13258-024-01522-w
36. Tong Z, Du X, Zhou Y, Jing F, Ma J, Feng Y, et al. Drp1-mediated mitochondrial fission promotes pulmonary fibrosis progression through the regulation of lipid metabolic reprogramming by ROS/HIF-1α. Cellular Signalling. 2024 May 1;117:111075.
37. Sun Z, Ji Z, Meng H, He W, Li B, Pan X, et al. Lactate facilitated mitochondrial fission-derived ROS to promote pulmonary fibrosis via ERK/DRP-1 signaling. J Transl Med. 2024 May 21;22(1):479.
38. Zhang J, Li W jing, Chen S qiang, Chen Z, Zhang C, Ying R, et al. Mutual promotion of mitochondrial fission and oxidative stress contributes to mitochondrial-DNA-mediated inflammation and epithelial-mesenchymal transition in paraquat-induced pulmonary fibrosis. World J Emerg Med. 2023;14(3):209–16.
39. Zheng C, Zhang L, Sun Y, Ma Y, Zhang Y. Alveolar epithelial cell dysfunction and epithelial-mesenchymal transition in pulmonary fibrosis pathogenesis. Front Mol Biosci [Internet]. 2025 Apr 24 [cited 2025 July 23];12. Available from: https://www.frontiersin.org/journals/molecular-biosciences/articles/10.3389/fmolb.2025.1564176/full
40. Chang EM, Chao CC, Wang MT, Hsu CL, Chen PC. PM2.5 promotes pulmonary fibrosis by mitochondrial dysfunction. Environmental Toxicology. 2023;38(8):1905–13.
41. Ma A, Feng Z, Li Y, Wu Q, Xiong H, Dong M, et al. Ferroptosis-related signature and immune infiltration characterization in acute lung injury/acute respiratory distress syndrome. Respir Res. 2023 June 10;24(1):154.
42. Wang L, Wang D, Zhang T, Ma Y, Tong X, Fan H. The role of immunometabolism in macrophage polarization and its impact on acute lung injury/acute respiratory distress syndrome. Front Immunol [Internet]. 2023 Mar 20 [cited 2025 July 23];14. Available from: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1117548/full
43. Hu H, Zhang W, Zhou Y, Zhao K, Kuang J, Liu X, et al. Engineered mitochondrial ROS scavenger nanocomplex to enhance lung biodistribution and reduce inflammation for the treatment of ARDS. Adv Compos Hybrid Mater. 2024 Oct 23;7(6):194.
44. Qiao X, Yin J, Zheng Z, Li L, Feng X. Endothelial cell dynamics in sepsis-induced acute lung injury and acute respiratory distress syndrome: pathogenesis and therapeutic implications. Cell Commun Signal. 2024 Apr 25;22(1):241.
45. The Potent Antitumor Activity of Smp43 against Non-Small-Cell Lung Cancer A549 Cells via Inducing Membranolysis and Mitochondrial Dysfunction [Internet]. [cited 2025 July 23]. Available from: https://www.mdpi.com/2072-6651/15/5/347

 doi:10.20944/preprints202508.0344.v1

46. Zhang L, Cui Y, Zhou G, Zhang Z, Zhang P. Leveraging mitochondrial-programmed cell death dynamics to enhance prognostic accuracy and immunotherapy efficacy in lung adenocarcinoma. J Immunother Cancer. 2024 Oct 24;12(10):e010008.
47. Wang Z, Li J, Wang L, Liu Y, Wang W, Chen J, et al. FFAR4 activation inhibits lung adenocarcinoma via blocking respiratory chain complex assembly associated mitochondrial metabolism. Cell Mol Biol Lett. 2024 Jan 19;29(1):17.
48. Ren X, Shi P, Su J, Wei T, Li J, Hu Y, et al. Loss of Myo19 increases metastasis by enhancing microenvironmental ROS gradient and chemotaxis. EMBO reports. 2024 Mar 12;25(3):971–90.
49. Ming H, Li B, Jiang J, Qin S, Nice EC, He W, et al. Protein degradation: expanding the toolbox to restrain cancer drug resistance. J Hematol Oncol. 2023 Jan 24;16(1):6.
50. Sun K, Zhi Y, Ren W, Li S, Zheng J, Gao L, et al. Crosstalk between O-GlcNAcylation and ubiquitination: a novel strategy for overcoming cancer therapeutic resistance. Exp Hematol Oncol. 2024 Nov 1;13(1):107.