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Review

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; chronic obstructive pulmonary disorder (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 uniquely 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]. These functions are essential not only for respiratory efficiency but also for protecting the organism against environmental insults, pathogens, and toxicants continually encountered in inhaled air. Mitochondria, as dynamic subcellular hubs, serve as the primary ATP source for these energetically costly processes, especially in energy-intensive lung cell types, and also finely regulate redox balance and signaling events essential for lung homeostasis and adaptive responses [4].

For instance, alveolar type II (ATII) cells depend on tightly regulated oxidative phosphorylation (OXPHOS) to sustain both the biogenesis and secretion of surfactant, a lipid-protein complex critical for reducing alveolar surface tension and ensuring optimal pulmonary mechanics. Deficiencies in mitochondrial ATP or quality control can disrupt surfactant production, compromising lung compliance and predisposing to atelectasis and respiratory failure [5]. ATII cells also orchestrate alveolar repair and regeneration after injury, two highly energy-dependent processes whose efficacy directly reflects mitochondrial health and metabolic flexibility [6].

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Ciliated epithelial cells require ATP to power ciliary beating for mucociliary clearance, a frontline defense against inhaled pathogens and particulate matter, thus maintaining airway sterility and preventing infection [7]. Recent evidence reveals that ciliated cells express high levels of mitochondrial uncoupling proteins (UCPs), which mitigate local ROS generation despite high respiratory activity, highlighting evolutionary adaptations that balance energy production and oxidative safety in the airway epithelium [8]. This coordinated ciliary motion is an exquisitely regulated process, sensitive to disruptions in cellular energy supply, underscoring the importance of mitochondrial function in epithelial barrier defense [9].

Additionally, immune cells such as alveolar macrophages depend on mitochondrial metabolism to fuel phagocytosis, cytokine production, and antigen presentation during inflammation and host defense against respiratory pathogens [10]. Mitochondrial bioenergetics are rapidly reprogrammed in activated macrophages to meet shifting demands between OXPHOS and glycolysis, contributing not just to energy supply but also to inflammatory phenotype polarization and tissue remodeling [11]. Endothelial cells lining the pulmonary vasculature similarly utilize mitochondrial ATP to maintain vascular integrity, regulate pulmonary blood flow, and modulate inflammatory signaling—all essential for efficient gas exchange and preventing vascular leakage [12-13].

These diverse and demanding metabolic requirements reflect evolutionary adaptations of pulmonary cells to the lung's unique microenvironment, characterized by steep oxygen gradients and frequent exposure to fluctuating oxygen tensions. The lungs face a paradoxical challenge, balancing the need for high oxygen utilization with protection against oxidative damage caused by ROS generated during mitochondrial respiration [14]. Lung mitochondria are strategically compartmentalized and equipped with quality control systems (fission, fusion, and mitophagy) to maintain functionality under stress and minimize damage from accumulated damage-associated molecular patterns (DAMPs), such as oxidized mitochondrial DNA, which can trigger inflammatory cascades and propagate tissue injury [15-16].

ATII cells maintain bioenergetic homeostasis even under hypoxia by balancing glycolysis and OXPHOS, allowing them to function during transient disruptions in oxygen availability [17]. In contrast, immune cells rapidly upregulate glycolysis during activation—a metabolic shift termed the "Warburg effect"—to satisfy biosynthetic and energetic demands in an inflammatory setting [18]. This capacity for metabolic plasticity, coordinated by mitochondrial network remodeling, enables lung cells to efficiently adapt to diverse physiological and pathological challenges, from infection to chronic injury or fibrotic stress [19-20].

Moreover, mitochondria act as signaling hubs integrating environmental cues and intracellular stress responses by regulating not only metabolic intermediates, ROS production, and calcium flux, but also innate immune sensing and inflammatory gene expression [21]. Therefore, mitochondrial dysfunction—whether by DNA damage, impaired quality control, or maladaptive ROS generation—can drive pathogenesis through both disrupted energy metabolism and unrestrained inflammation [3-4, 6].

The goal of this review is to provide a timely and comprehensive synthesis of recent advances (January 2023 to June 2025) on how mitochondrial dysfunction underlies the pathogenesis of lung diseases, with a special focus on the molecular intersection between mitochondrial biology, inflammation, fibrosis, apoptosis, and tumorigenesis. By summarizing the latest research, this review addresses the urgent need for up-to-date guidance where both our understanding of mitochondrial complexity and the landscape of potential therapeutic interventions are rapidly expanding.

In this review, we summarize recent work examining how disruptions in mitochondrial dynamics—including fusion and fission—bioenergetics, quality control mechanisms such as mitophagy, and the regulation of ROS production contribute to cellular and molecular abnormalities underlying lung diseases such as asthma, COPD, IPF, ARDS, and lung cancer. We further discuss how advances in mitochondrial biology are illuminating novel therapeutic windows, with mitochondria-targeted interventions poised to transform prevention and treatment strategies across the spectrum of pulmonary diseases.

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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.

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:

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- 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.

Despite efforts to reduce selection bias, limited access to paywalled full texts may have constrained thorough data extraction in certain segments of the literature. Furthermore, assessment of study quality was narrative rather than using formal risk-of-bias tools, potentially introducing reviewer subjectivity. Finally, by focusing on the last 2.5 years, this review might underrepresent the historical context critical for understanding certain mechanistic advances.

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 [21-23]. 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 [24-25]. 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 [26]. In pulmonary fibrosis, excessive fission promotes fibroblast proliferation via mtROS-TGF-β signaling [27]. Furthermore, collapse of the mitochondrial membrane potential triggers the opening of mitochondrial permeability transition pore (MPTP), precipitating apoptosis or necrosis in alveolar cells [28]. Lastly, mtDNA mutations impair electron transport chain (ETC) function, perpetuating metabolic inefficiency and inflammation [29]. These dysfunctions converge to impair cellular homeostasis, exacerbate oxidative stress, and promote pathological processes such as apoptosis, senescence, and pro-fibrotic signaling.

Recent evidence suggests that mitochondrial dysfunction in pulmonary tissues also modulates intracellular calcium handling and disrupts mitochondrial–nuclear communication, contributing to altered gene expression and metabolic reprogramming [30]. For instance, disturbed Ca^{2+} cycling due to defective mitochondria can enhance susceptibility to hypoxic injury and sensitize cells to environmental stressors such as particulate matter [31]. Crosstalk between mitochondria and other organelles, such as the endoplasmic reticulum (ER), plays a crucial role in modulating cell fate in lung tissues, with altered mitochondrial–ER contact points implicated in disease progression, particularly in ARDS and lung cancer [32-33]. Epigenetic modifications, including mitochondrial DNA methylation and acetylation of metabolic enzymes further add layers of complexity, especially as they interact with environmental factors like smoking or pollution [34]. 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

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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.

Emerging translational studies have begun testing small molecule modulators, gene therapies, and even mitochondrial transplantation as strategies to ameliorate mitochondrial defects in preclinical lung disease models [35-36]. Early-phase clinical trials published during the review period have evaluated mitochondrial-targeted antioxidants or metabolic modulators, with preliminary evidence of efficacy in subsets of patients with COPD and IPF [37-39]. These translational efforts underscore the rapid evolution of the field and the drive toward harnessing mitochondrial biology for disease modification.

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 [40-41]. 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 [42]. ARDS is marked by mitochondrial damage in endothelial cells, exacerbating vascular leakage [43]. 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 [44]. Lastly, lung cancer cells exhibit a remarkable metabolic plasticity, often undergoing mitochondrial reprogramming even in normoxic conditions. This metabolic rewiring provides these rapidly proliferating cells with a bioenergetic advantage, enabling the generation of essential biosynthetic precursors and ATP to fuel their aggressive growth [7]. Notably, new research highlights the potential for combinatorial approaches using mitochondrial modulators alongside established therapies. For example, preclinical models of lung cancer and IPF show improved outcomes when mitochondrial-targeted agents are administered with standard anti-fibrotic or chemotherapeutic drugs, suggesting possible synergistic effects [45-46]. Additionally, mitochondrial biomarkers—such as circulating mtDNA or mitophagy-related proteins—are being investigated as predictive indicators of therapeutic response, potentially paving the way for precision medicine strategies in respiratory illness [47-50].

Therapeutic implications include mitochondrial-targeted antioxidants (MitoQ), ETC modulators, and regulators of dynamics (e.g. DRP1 inhibitors) [51-52]. 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 [53]. 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 [54-55]. Increased ROS production by dysfunctional mitochondria amplifies oxidative stress in airway epithelial cells, further promoting inflammation and tissue damage.

Recent advances shed light on mitochondrial involvement in airway remodeling, a key pathological aspect of chronic asthma [56-57]. Mitochondrial dysfunction in bronchial smooth muscle cells contributes to hyperplasia and hypertrophy, exacerbating airway narrowing [58]. Furthermore, mitochondrial DNA released during allergic airway inflammation may act as a damage-associated molecular pattern (DAMP), triggering innate immune responses and perpetuating chronic inflammation [59-60]. Mitochondria-derived peptides, such as humanin, have been identified with potential protective roles against oxidative damage in asthma, although their precise function requires further elucidation [61]. Innovative research is exploring the repurposing of established drugs, such as metformin, for their mitochondrial-stabilizing and anti-inflammatory effects in asthma [62-63]. Ongoing clinical trials are evaluating inhaled antioxidants designed specifically to target mitochondrial sources of ROS.

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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 [64]. 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 [65-67]. 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 [68-69].

Additionally, COPD patients exhibit altered mitochondrial dynamics in airway macrophages, impairing their ability to resolve inflammation and respond to infection [70]. A recent study reported associations between mitochondrial dysfunction and exacerbation frequency, as well as correlation with clinical severity and lung function decline [71]. Mitochondrial abnormalities in skeletal muscle contribute to comorbidities such as cachexia and fatigue in COPD [72]. Researchers are now investigating mitochondrial-targeted therapies (e.g., peptide-based antioxidants, gene therapies to enhance mitophagy) not only to address pulmonary dysfunction but also to improve overall patient fitness and quality of life [73]. Advances in non-invasive imaging techniques, such as PET tracers for mitochondrial function, are enabling longitudinal monitoring in clinical trials [74-75].

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 [51, 76]. 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 [52, 77-78]. Additionally, oxidative stress from elevated mtROS levels promotes ECM deposition through TGF-β signaling pathways [79].

Recent single-cell transcriptomic analyses have revealed cell-type specific patterns of mitochondrial dysfunction within fibrotic lungs, such as heightened susceptibility of type II alveolar epithelial cells to mitochondrial depolarization [57]. Dysregulated mitochondrial metabolism in fibroblasts leads to excess lactate production and extracellular acidification, fostering a pro-fibrotic microenvironment and further ECM accumulation [80]. Mitochondrial transfer between mesenchymal cells and macrophages has been observed, possibly modulating immune responses and tissue remodeling [81]. These discoveries are driving novel therapeutic concepts, including mitochondrial transplantation or modulation of metabolic intermediates, as emerging strategies against fibrosis [82]. Gene editing approaches targeting regulators of mitochondrial biogenesis are under preclinical investigation for their anti-fibrotic potential [83].

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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 [84]. Impaired mitophagy further exacerbates mitochondrial dysfunction in fibrotic lungs [85]. 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 [42]. 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 [86]. 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 [87].

Recent work demonstrates that mitochondrial DAMPs released into circulation during ARDS can act as potent inducers of systemic inflammation and multi-organ dysfunction [88]. Modified plasma mtDNA levels serve as prognostic biomarkers for disease severity and likelihood of mechanical ventilation [89]. Animal models have shown that mitochondrial-targeted therapies can reduce alveolar epithelial and endothelial barrier damage, decrease pulmonary edema, and improve survival rates [90]. Enhancing mitochondrial biogenesis using pharmacological agents or PGC-1α agonists is currently an area of high interest, as is stem cell therapy with attention to their mitochondrial donor/recipient dynamics [91]. Precision approaches tailored to the patient's mitochondrial injury profile may ultimately improve ARDS management.

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 [92]. 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 [93-95]. Tumor cells often exhibit reprogrammed metabolism characterized by increased glycolysis (Warburg effect) alongside functional ETC activity to support rapid proliferation [18]. This metabolic reprogramming is facilitated by alterations in mitochondrial dynamics and biogenesis.

Comprehensive genomic profiling of lung tumors has revealed a high frequency of mutations not only in nuclear oncogenes but also in mtDNA, correlating with aggressive behavior and treatment resistance [96-97]. Advances in metabolic imaging allow for in vivo assessment of mitochondrial function, facilitating personalized selection of metabolic inhibitors for patient subgroups [98]. Recent research into the tumor microenvironment highlights mitochondrial interplay between cancer-associated fibroblasts and cancer cells, promoting metabolic symbiosis and immune evasion [99-100]. Clinical trials are underway evaluating mitochondria-specific prodrugs and epigenetic modulators, some showing early promise in overcoming resistance to kinase inhibitors and immune checkpoint blockade [101].

Mitochondrial dysfunction also promotes metastasis by enhancing cellular motility through ROS-mediated signaling pathways [102]. Furthermore, mutations in mtDNA can confer resistance to chemotherapy by altering apoptotic pathways or increasing drug efflux mechanisms [103-104].

Strategies targeting mitochondrial metabolism present promising therapeutic opportunities in lung cancer. Agents like ETC inhibitors or modulators of mitochondrial dynamics could selectively

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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.

A key insight emerging from recent studies is the disease- and cell type-specific adaptation of mitochondrial networks in response to chronic injury. For example, airway epithelial cells and alveolar macrophages respond differently to mitochondrial stress, leading to varying patterns of inflammation and tissue remodeling across diseases. Mitochondrial abnormalities interplay with the extracellular matrix, immune cell function, and microenvironmental oxygen gradients, adding further complexity to their role in pathogenesis. Importantly, mitochondrial interactions with other organelles, such as the ER, peroxisomes, and lysosomes, modulate responses to xenobiotic exposure, infection, and fibrogenic signals, highlighting the integrated nature of cellular stress responses in the lung.

Recent advances in high-throughput 'omics' technologies—such as single-cell RNA sequencing and metabolomics—have enabled detailed dissection of mitochondrial signatures in human lung specimens, animal models, and patient-derived organoids. This has facilitated the identification of novel biomarkers and potential therapeutic targets, particularly those regulating mitochondrial biogenesis, fusion/fission balance, and mitophagy. These technologies also provide unprecedented resolution in tracking clonal expansion of mtDNA mutations, revealing how somatic mitochondrial genomic alterations may drive disease heterogeneity 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 responses, while in lung cancer, mitochondrial reprogramming enables tumor cells to meet the energy and biosynthetic demands of uncontrolled proliferation.

Comparative analyses have uncovered that while certain mechanisms (such as impaired biogenesis and enhanced fission) are shared across diseases, others are more specific. For example, the involvement of mtDNA as a DAMPs is particularly pronounced in ARDS, while the role of mitochondrial metabolic flexibility to evade apoptosis is a hallmark of lung cancer. This specificity may be clinically useful for differential diagnosis and personalized therapy development.

Moreover, mounting evidence indicates that environmental and lifestyle factors—including air pollution, nutrition, and physical activity—modulate mitochondrial vulnerability in pulmonary tissues. Epigenetic regulation, including DNA methylation and histone modification of mitochondrial genes, further modulates disease trajectory, opening new possibilities for preventive strategies. The impact of aging on mitochondrial quality control also highlights the importance of considering patient age and comorbidities in both research and clinical management.

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

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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.

Clinically, a new wave of early-phase trials is exploring the utility of mitochondrial-targeted agents as adjuncts with standard-of-care treatments in COPD, IPF, and lung cancer. Advances in drug delivery, such as the development of nanoparticles and mitochondria-penetrating peptides, are improving tissue specificity and minimizing off-target effects. Preclinical studies support the notion that combining mitochondrial-targeted drugs with conventional anti-inflammatory, anti-fibrotic, or chemotherapeutic agents may exert synergistic effects and enhance treatment efficacy. In oncology, for instance, coupling metabolic modulators with immune checkpoint inhibitors is being evaluated to overcome immune evasion and drug resistance.

Biomarker development is also progressing; circulating mtDNA levels, mitochondrial gene expression signatures, and metabolic flux assays are increasingly recognized as potential markers of disease activity, prognosis, and treatment response. Such biomarkers could be integrated into precision medicine frameworks to individualize mitochondrial therapy based on specific molecular or functional defects identified in patients.

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.

Regulatory and safety considerations, including off-target metabolic effects and potential toxicity, are critical aspects that require careful assessment in ongoing and future trials. Moreover, multidisciplinary collaborations between pulmonologists, cell biologists, pharmacologists, and bioengineers are essential to accelerate the path from mechanistic discovery to clinical application.

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. The review's time frame may also have missed notable studies published shortly after June 2025 or significant milestones reached in ongoing clinical trials. Furthermore, some potentially relevant experimental reports may have been excluded if they did not explicitly highlight mitochondrial endpoints, despite contributing to our understanding of related pathways. The narrative risk-of-bias assessment, although informed by best practices, is inherently qualitative and may not fully account for heterogeneity in study quality. Lastly, animal and in vitro findings may not fully extrapolate to human disease due to inherent species differences or limitations in model systems.

Future research should address several key gaps:

- Elucidating the interplay between mitochondrial dysfunction and genetic/epigenetic factors predisposing individuals to lung disease.

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- 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.

Other important directions include unraveling mitochondrial crosstalk with the lung microbiome, investigating the impacts of early-life exposures on mitochondrial health and later disease risk, and leveraging artificial intelligence to integrate multi-omics data for personalized medicine. The application of gene editing technologies, such as CRISPR/Cas9, in correcting mitochondrial genomic mutations also represents an exciting frontier for future therapeutic research.

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.

In addition, a mitochondrial approach has the potential to inform public health strategies aimed at minimizing environmental risk factors—such as air pollution and smoking—known to impair mitochondrial health. Educational initiatives that promote lifestyle modifications (e.g., regular exercise, balanced nutrition) could also contribute to the preservation of mitochondrial function and, ultimately, lung wellness across the lifespan.

5. Conclusion

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. The coming years will likely see rapid advancements in the application of precision mitochondrial therapies, spanning from antioxidants and gene modulators to cell-based and regenerative approaches. The integration of robust biomarkers and longitudinal patient monitoring will help tailor these interventions, maximizing therapeutic benefit while minimizing adverse effects.

A holistic focus on mitochondrial health, extending from basic science to clinical care and public health, may ultimately transform the management of major pulmonary diseases. Unlocking the full therapeutic potential of mitochondria will require sustained investment in research, multidisciplinary collaboration, and inclusive global initiatives to ensure that advances are accessible to diverse patient populations. By embracing the centrality of mitochondrial biology, the scientific and clinical community can move closer to realizing personalized, mechanism-based prevention and treatment of lung disease.

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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

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