Thesis

Evaluating the Role of Sirtuins in the Pathogenesis of Chronic Obstructive Pulmonary Disease

submitted by

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Graz, October 11, 2025 Nihal Simsek

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Zusammenfassung

Die chronisch obstruktive Lungenerkrankung (COPD) ist eine fortschreitende Lungenerkrankung, die durch eine persistierende Atemwegsobstruktion, chronische Entzündungsprozesse und strukturelle Veränderungen des Lungengewebes gekennzeichnet ist. Die Pathophysiologie der COPD ist durch komplexe Wechselwirkungen zwischen Immunmechanismen und nicht-immunologischen Prozessen charakterisiert, welche die Entstehung einer chronischen Bronchitis, eines Lungenemphysems und systemischer Komorbiditäten begünstigen.

Die vorliegende Arbeit untersucht die Rolle der Sirtuine im pathophysiologischen Geschehen der COPD. Dabei wird insbesondere der Einfluss der Sirtuine auf die relevanten Signalwege beleuchtet. Die Sirtuin-Proteine 1 bis 7 (SIRT1-7) sind evolutionär konservierte Deacetylasen, die sich hinsichtlich ihrer subzellulären Lokalisation und spezifischen Funktion unterscheiden. Insbesondere SIRT1, SIRT3 und SIRT6 haben sich unter anderem als zentrale Regulatoren von Entzündungsprozessen, DNA-Reparaturmechanismen und mitochondrialer Funktion herauskristallisiert, welche entscheidende Schlüsselmechanismen in der Entstehung und das Fortschreiten der COPD darstellen.

Die methodische Grundlage dieser Arbeit bildet ein narratives Literaturreview, das wissenschaftliche Publikationen der letzten sechs Jahre berücksichtigt. Analysiert wurden experimentelle Modelle und Studien, die den Zusammenhang zwischen der Regulation von Sirtuinen und der Pathogenese der COPD untersuchen. Die Literaturrecherche erfolgte über die Datenbanken PubMed, Google Scholar und ClinicalTrials.gov sowie unter Einbeziehung der aktuellen Leitlinien der Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Die Auswertung ergibt, dass Sirtuine keine passiven Biomarker des Krankheitsverlaufs sind, sondern aktive Akteure im pathophysiologischen Geschehen. Die gezielte Modulation dieser Prozesse bildet eine Basis für individualisierte, zukünftige Behandlungsstrategien, die der Heterogenität der COPD gerecht werden könnten.

Die vorliegende Arbeit trägt zur Entwicklung eines Verständnisses von Sirtuinen als molekulare Brücken zwischen den Bereichen Alterung, Stoffwechsel und Entzündung bei. Sie eröffnet neue Perspektiven hinsichtlich potenzieller, krankheitsmodifizierender Therapien für chronische Atemwegserkrankungen.

Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition characterized by persistent airflow limitation, chronic inflammation, and structural lung damage. COPD is a leading cause of global morbidity and mortality. Major risk factors include exposure to tobacco smoke, air pollution, occupational hazards, and genetic predispositions. The pathophysiology of COPD involves complex interactions between immune and non-immune mechanisms. These processes contribute to chronic bronchitis, emphysema, and systemic comorbidities.

This thesis explores the role of sirtuins in the molecular landscape of COPD, emphasizing their involvement in key pathological pathways. Sirtuins 1 through 7 (SIRT1-7) are evolutionarily conserved proteins with distinct subcellular localizations and functional roles. In particular, SIRT1, SIRT3, and SIRT6 are central regulators of inflammation, redox homeostasis, DNA repair, and mitochondrial function, all of which are processes that are deeply implicated in COPD progression. However, depending on disease stage, cell type, and environmental context, certain sirtuins can act as both protective mediators and contributors to tissue damage.

A narrative literature review was conducted using peer-reviewed publications from the past six years. The review focused on experimental models, mechanistic studies, and emerging therapeutic strategies related to sirtuins in respiratory diseases. The review utilized databases such as PubMed, Google Scholar, and ClinicalTrials.gov, as well as guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

The synthesis reveals that sirtuins are active participants, not passive biomarkers, in COPD pathogenesis. Modulating them offers promising avenues for future therapies.
Although most current interventions are in the preclinical stage, they lay the groundwork for precision medicine approaches that could address COPD's heterogeneity.

This work advances the evolving understanding of sirtuins as molecular bridges between aging, metabolism, and inflammation. It offers novel insights into potential disease-modifying therapies for chronic respiratory diseases.

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List of Abbreviations

COPD	chronic obstructive pulmonary disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IL	interleukin
ROS	reactive oxygen species
NF-κB	nuclear factor kappa B
NLRP3	nod-like receptor protein 3
DNA	deoxyribonucleic acid
SASP	senescence-associated secretory phenotype
NAD^+	nicotinamide adenine dinucleotide
FEV_1	forced expiratory volume in one second
LABA	long-acting β2-agonist
LAMA	long-acting muscarinic antagonist
SIRT	sirtuin
PGC-1α	peroxisome proliferator-activated receptor-γ coactivator-1α
FOXO	forkhead box transcription factors
NADH	nicotinamide-adenine dinucleotide
ADP	adenine diphosphate
SOD	superoxide dismutase
RNA	ribonucleic acid
CSE	cigarette smoke extract
CS	cigarette smoke
PM	particulate matter
MAPK	mitogen-activated protein kinase
Nrf2	nuclear factor erythroid 2-related factor 2
MnSOD	manganese superoxide dismutase
miRNA	micro-RNA
PI3K	phosphoinositide 3-kinase
AKT	protein kinase B
mTOR	mammalian target of rapamycin
ER	endoplasmatic reticulum
NMN	nicotinamide mononucleotide

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1. Introduction

1.1. Understanding the Basics of COPD

1.1.1. Definition

Chronic obstructive pulmonary disease (COPD) is a term used to describe a progressive, irreversible respiratory condition marked by chronic airflow limitation, systemic inflammation, and structural damage to the lungs (1).
The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD in its 2024 report as "a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction" (1).

1.1.2. Epidemiological Data

COPD constitutes a substantial global health burden, contributing to considerable morbidity and mortality on a global scale (2). The condition's high prevalence, chronic progressive nature, and frequent exacerbations necessitate ongoing management, long-term medication use, and often hospitalization. These factors contribute to substantial healthcare costs and resource utilization (3).

According to the Global Burden of Disease Study 2019, COPD has already been observed to impact 15% of men and 8% of women worldwide, which makes approximately 212 million people globally (3). It marks the third leading cause of death after ischemic heart disease and stroke (5).

Within the European Union, the financial burden of COPD is significant, accounting for 56% of the total cost of respiratory diseases. This amounts to €38.6 billion annually (3). Despite the progress in the field of COPD diagnosis and management, the phenomenon of underdiagnosis persists as a salient issue, with research indicating that 50-80% of COPD cases remain undetected, particularly in the early stages of the disease (1).
Projections from a modeling study indicate a 23% increase in the global prevalence of COPD cases among individuals aged 25 and older between the years 2020 and 2050. This finding

suggests that the global prevalence of COPD is predicted to reach approximately 600 million by the year 2050 (3).
These trends underscore the pressing need for targeted public health interventions and enhanced diagnostic strategies to address the escalating global burden of COPD.

1.1.3. Etiological Origins and Risk Factors

COPD is a multifactorial disease with etiological origins rooted in genetic predispositions, environmental exposures, and the natural progression of age (6).

The GETomics concept was introduced in this context to contribute to this complex fact of development. The risk factors under consideration are classified as follows: G for genetics, E for environmental, and T for lifetime with age of the individual and disease history (7).

Genetics

Genetic predisposition is one of the most well-established contributors (8).
The most recognized genetic risk factor is α1 antitrypsin deficiency, a hereditary condition caused by mutations in the SERPINA1 gene. It leads to reduced levels of the protein α1 antitrypsin, that protects lung tissue from degradation by enzymes like neutrophil elastase. This results in unopposed neutrophil elastase activity, causing early-onset emphysema even in the absence of significant environmental exposures (9).
Besides, genome-wide association studies (GWAS) have identified 82 loci as candidate genes, which are associated with altered lung development, inflammation, and oxidative stress responses, further modulating disease risk and severity. HHIP, FAM13A, and AGER have been identified as the most replicable COPD GWAS loci (10,11).

Smoking history

The predominant etiological agent on a global scale is tobacco smoke exposure. In high-income countries, tobacco smoking accounts for over 70% of COPD cases (12). Cigarette smoke contains more than thousands of toxic and oxidative agents that trigger a series of physiological responses, including chronic inflammation. These responses, when sustained over time, can culminate in irreversible lung damage (1).
While not all smokers develop COPD, prolonged exposure significantly increases the risk (13). Secondhand smoke exposure constitutes an additional significant contributor, particularly in non-smokers who develop COPD (14).

Recent findings also indicate that e-cigarettes and vaping may present novel risks to lung health, though their long-term implications for the development of COPD require further examination (15).

Environment

Environmental exposures play a significant role in the development and progression of COPD, particularly in Low- and Middle-Income Countries (12).

Air pollution from biomass fuel combustion remains a major risk factor. Occupational exposures to dust, fumes, and chemicals in industries like mining, construction, and agriculture further increase COPD risk, particularly among workers without adequate protective measures (16). Climate change is expected to worsen these environmental risks by increasing air pollution levels and the frequency of respiratory infections (17).

Age

Age is a critical factor in the epidemiology of COPD, as the disease predominantly affects individuals over the age of 40. The global median age is 65 years (18).

The prevalence of COPD increases with advancing age due to cumulative exposure to risk factors such as smoking, environmental pollutants, and natural lung function decline (19). Aging also contributes to reduced lung elasticity, impaired repair mechanisms, and increased susceptibility to oxidative stress, all of which exacerbate the progression of COPD (20).

Early-life respiratory insults, such as low birth weight, prematurity, childhood respiratory infections, and poor nutrition, can impair maximal lung growth and lead to reduced pulmonary reserve, increasing the risk of developing COPD later in life (21).

Sex

Sex differences in COPD have become increasingly apparent over the past decade, with women now representing a growing proportion of affected individuals (22). Historically, COPD was more prevalent in men due to higher smoking rates, but this trend has shifted as smoking prevalence among women has risen in many regions (23).

Women are also biologically more susceptible to the harmful effects of cigarette smoke and biomass fuel exposure, leading to faster lung function decline and more severe symptoms compared to men (24).

1.1.4. Symptoms and COPD Progression

The symptoms of COPD develop over the course of months (25).

Early Symptoms

In the early stages of COPD, symptoms are often mild and may be dismissed as signs of aging or being out of shape (26).

The early hallmark symptom is a chronic cough, often referred to as a smoker's cough accompanied by copious amounts of phlegm. This cough is persistent and typically worsens in the morning (27). Individuals may experience dyspnea during physical activities. Wheezing, a whistling sound during breathing, and occasional chest tightness may also occur, though these symptoms are often intermittent (28). Fatigue is another common early symptom, as reduced lung function forces the body to work harder to breathe (29). Despite these signs, many individuals remain undiagnosed at this stage because symptoms do not significantly interfere with daily life (1).

Moderate Symptoms

As COPD progresses to the moderate stage, symptoms become more pronounced and begin to interfere with daily activities (30). Dyspnea becomes more frequent and occurs even with mild exertion. The chronic cough persists, and mucus production increases, often becoming thicker and more difficult to clear (31). Patients may notice a decline in their ability to engage in physical activities due to worsening breathlessness. Frequent respiratory infections are common and may exacerbate symptoms temporarily (32).

Some individuals may experience unintentional weight loss due to the increased energy expenditure required for labored breathing (33).

At this stage, patients often seek medical attention, leading to diagnosis through spirometry (1).

Severe Symptoms

In the severe stage of COPD, symptoms significantly impair quality of life and daily functioning (34).

Severe dyspnea is a constant issue, occurring even at rest and making simple tasks like dressing or bathing challenging (35). The increased breathing effort in advanced emphysema leads to weight loss known as pulmonary cachexia (33). Patients may develop cyanosis due

to chronically low oxygen levels in the blood. Barrel chest, caused by hyperinflation of the lungs, becomes noticeable (36). Some patients may experience edema in the ankles, feet, or legs due to fluid retention associated with Cor pulmonale (37). Frequent and severe exacerbations are common, often requiring hospitalization (10). Older adults with COPD often experience more severe symptoms (1).

Exacerbations

COPD exacerbations are acute episodes of symptom worsening that go beyond normal day-to-day variability and often require additional treatment (38). These episodes are triggered by factors such as viral or bacterial respiratory infections (39). During exacerbation, patients experience a marked increase in dyspnea, often accompanied by a worsening cough and significant change in sputum characteristics, such as thickness or purulence (40). Systemic symptoms like fever may also occur. They are marked by a worsening of the patient´s overall condition (41).

Exacerbations are classified as mild, moderate, or severe based on the level of intervention required (42). Mild exacerbations can often be managed at home with increased use of bronchodilators, while severe exacerbations may necessitate hospitalization for treatment (43).

Exacerbations accelerate lung function decline, reduce quality of life, and increase mortality risk, making their prevention and management a critical component of COPD care (1).

1.1.5. Pathophysiological Alterations

COPD is characterized by progressive and irreversible pathophysiological alterations, primarily chronic inflammation, airway obstruction, and parenchymal destruction (44).

The disease encompasses two overlapping pathological conditions: Chronic bronchitis, which is defined by persistent inflammation of the bronchial walls, and emphysema, which is marked by alveolar septal degradation (45).

Prolonged exposure to noxious substances, particularly cigarette smoke, triggers neutrophilic infiltration, cytokine release, and hyperplasia of mucus-secreting glands in chronic bronchitis. This leads to excessive mucus production, ciliary dysfunction, and narrowed airways (46). The remodeling process results in the loss of cilia function and the transformation of the respiratory epithelium from ciliated cells to squamous epithelium, with a concomitant increase in serous and mucous glands. Consequently, mucociliary clearance

is impaired, which compromises normal airway function and mucus transport (47). The inability to clear the mucus effectively then leads to airway obstruction. While a vigorous cough can partially facilitate mucus clearance, it also contributes to airway wall damage and smooth muscle hypertrophy (48). This in turn further exacerbates airflow limitation and promotes the development of pulmonary emphysema (19).

In emphysema, proteases released by activated macrophages and neutrophils play a key role in tissue destruction (49). These proteases overwhelm the body's natural protease inhibitors, resulting in unchecked degradation of lung tissue. The destruction of alveolar septa and the breakdown of extracellular matrix components lead to the enlargement of air spaces. The structural loss reduces the alveoli's surface area and capacity for gas exchange, while diminished elastic recoil causes air trapping and hyperinflation (50). Structural remodeling, including peribronchial fibrosis and airway thickening, further aggravates obstruction (4).

Systemic manifestations of COPD include skeletal muscle wasting, driven by systemic inflammation and oxidative stress, as well as pulmonary hypertension, which results from chronic hypoxia-induced vasoconstriction and vascular remodeling (51). Others include cardiovascular diseases such as heart failure and ischemic heart disease; osteoporosis, which is linked to inflammatory cytokines and corticosteroid use; and metabolic disturbances, like insulin resistance and unintentional weight loss (52).

1.1.6. Core Mechanisms

COPD is driven by complex mechanisms interactions. Below is a general classification of core mechanisms, focusing on immune and non-immune components.

1.1.6.1. Immune Mechanisms

Inflammation in COPD is characterized by the infiltration of innate and adaptive immune cells, including macrophages, neutrophils, and cytotoxic T-lymphocytes, which release pro-inflammatory mediators, e.g., tumor necrosis factor α (TNF-α), Interleukin-6 (IL-6), IL-8, proteases, and reactive oxygen species (ROS). These components synergistically damage lung tissue, leading to emphysema and chronic bronchitis (53).

Key pathways such as nuclear factor- kappa B (NF-κB) and the nod-like receptor protein 3 (NLRP3) inflammasome amplify inflammation by driving cytokine production and activating pyroptotic cell death (54). Oxidative stress further exacerbates inflammation by

inactivating antiproteases, like α1 antitrypsin, impairing antioxidant defenses, and generating damage-associated molecular patterns (DAMPs) that perpetuate immune activation (55). The result is a self-sustaining cycle of tissue injury, impaired repair, and progressive airflow limitation (56).

It has been shown that there is a potential link between autoimmunity and the pathogenesis of COPD, suggesting that a breakdown in immune tolerance to self-antigens may play a role (57). Chronic exposure to environmental pollutants can trigger the release of neo-antigens, such as oxidised proteins, elastin fragments and post-translationally modified proteins. These are recognised as "non-self" by the immune system. This process results in the production of autoantibodies, including anti-elastin and anti-epithelial cell antibodies (58). Furthermore, it has been demonstrated that this process can lead to the activation of autoreactive T-cells, including CD4+ Th1/Th17 and CD8+ cytotoxic T-cells (59). These autoreactive responses perpetuate lung injury by targeting structural proteins, including collagen, elastin and epithelial cells, exacerbating tissue destruction and fibrosis (60).

The processes of molecular mimicry and epitope spreading serve to further amplify autoimmune-driven inflammation. Molecular mimicry is the phenomenon in which microbial antigens cross-react with self-antigens. Epitope spreading is the phenomenon in which hidden self-antigens become exposed during tissue damage (61).

Dysbiosis is defined as an imbalance in the composition and function of microbial communities (62). In the lungs, the airway microbiome undergoes a shift from a balanced state dominated by commensal Firmicutes and Bacteroidetes to an overgrowth of pathogenic Proteobacteria, including Haemophilus, Moraxella, and Pseudomonas, accompanied by a reduction in microbial diversity (63). Pathogenic bacteria release virulence factors, including lipopolysaccharides and proteases, which activate Toll-like receptors on macrophages and epithelial cells. This, in turn, triggers NF-κB-mediated inflammation and neutrophil recruitment (64), which can exacerbate airway inflammation and tissue destruction (65).

1.1.6.2. Non-immune Mechanisms

Cellular senescence is a state of irreversible cell cycle arrest driven by deoxyribonucleic acid (DNA) damage, oxidative stress, or telomere shortening (66).

Chronic exposure to environmental pollutants has the capacity to induce senescence in lung epithelial cells, fibroblasts, and immune cells, including alveolar macrophages (9). The

process of senescence in cells is accompanied by the adoption of a senescence-associated secretory phenotype (SASP). The release of pro-inflammatory cytokines (IL-6, IL-8), matrix metalloproteinases (MMPs), and ROS is a hallmark of this process, leading to chronic inflammation, tissue remodeling and alveolar destruction (67).

Airway remodeling is a maladaptive structural alteration of the airways driven by chronic inflammation, oxidative stress, and repetitive injury (68). Key features include epithelial metaplasia, smooth muscle hypertrophy and hyperplasia, and emphysema (57). The transition of fibroblasts to a pro-fibrotic phenotype is resulting in the secretion of collagen and fibronectin. This process contributes to the thickening of airway walls and the narrowing of lumens (69).

1.1.6.3. Hybrid Mechanisms

Oxidative stress is defined as an imbalance between the production of ROS and the body's antioxidant defenses (70). It amplifies inflammation by activating NF-κB and NLRP3 inflammasomes, driving cytokine release and neutrophil recruitment (71). Prolonged exposure to environmental pollutants results in the introduction of exogenous ROS, including superoxide and hydroxyl radicals. Endogenous ROS are generated from activated inflammatory cells, such as neutrophils and macrophages, via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and mitochondrial dysfunction (72). ROS damage lipids, proteins, and DNA, impairing cellular function and perpetuating protease-antiprotease imbalance, leading to unchecked elastase activity and emphysema (73).

Mitochondrial dysfunction is driven by chronic exposure to oxidative stress (74). Impaired mitochondrial electron transport chain activity leads to excessive ROS leakage, reduced adenosine triphosphate (ATP) production, and accumulation of damaged mitochondrial DNA (63). Cigarette smoke directly disrupts mitochondrial complexes, while ROS further damage mitochondrial DNA and proteins, creating a self-perpetuating cycle of oxidative damage (75). Dysfunctional mitochondria results in apoptotic cell death, chronic inflammation and NLRP3 inflammasome activation (54). Additionally, metabolic reprogramming toward glycolysis depletes nicotinamide adenine dinucleotide (NAD^+), exacerbating mitochondrial inefficiency and energy deficits (76).

Protease-antiprotease imbalance is an imbalance between enzymes that degrade the extracellular matrix within the lung and proteins that oppose this process. In healthy lungs,

antiproteases such as α1-antitrypsin neutralize proteases that are released during inflammation (77). Persistent exposure to cigarette triggers the release of excessive proteases, while concurrent oxidative stress deactivates antiproteases. This imbalance allows proteases to degrade elastin, collagen, and other extracellular matrix components in alveolar walls and airways, resulting in emphysema and airway remodeling (78). Specifically, the proteases neutrophil elastase, MMP-9, and MMP-12 play a crucial role in the degradation of elastin, mucus hypersecretion and the breakdown of the extracellular matrix (79). Genetic α1 antitrypsin deficiency or smoke-induced α1 antitrypsin dysfunction has been demonstrated to exacerbate this imbalance, accelerating lung destruction (77).

Dysregulated autophagy is characterized by a disruption in the process of autophagy, leading to either excessive or defective clearance of damaged organelles, such as mitochondria and proteins. In immune cells, defective autophagy reduces the clearance of apoptotic cells, thereby sustaining chronic inflammation (9). This dysregulation has been demonstrated to shift autophagy from a protective mechanism to a driver of cellular senescence, airway remodeling, and emphysema (77).

1.1.7. Diagnostics

The diagnosis of COPD is made through a combination of clinical evaluation, spirometry testing, imaging, and ruling out other possible diagnoses (1).

The initial step in the clinical evaluation of a patient is the compilation of a comprehensive medical history. This history should emphasize chronic symptoms such as dyspnea, cough, and sputum production, as well as exposure to known risk factors (80).

A physical examination may reveal signs of chronic lung hyperinflation, such as cyanosis and a barrel-shaped chest, which are particularly evident in advanced emphysema. Auscultation may detect wheezing, whistling, or humming sounds commonly associated with chronic bronchitis. In cases with associated comorbidities, relevant clinical signs may also be present. For instance, peripheral edema may be indicative of decompensated Cor pulmonale (81).

Spirometry is the gold-standard test for confirming persistent airflow limitation. It proves airflow limitation by demonstrating a post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of less than 0.70. This measurement aids in identifying dyspnea and allows for classification into different stages of disease severity (82).

In addition to spirometry, body plethysmography is often used to evaluate lung volumes, airway resistance, and maximal respiratory effort. This provides more information about the extent of pulmonary impairment (80).
Additional tests include screening for α1 antitrypsin deficiency in young or nonsmoking patients, arterial blood gas analysis to determine the presence of hypoxemia and hypercapnia, and pulse oximetry (83).
Chest imaging, including X-rays or CT scans, helps rule out other conditions, such as heart failure or lung cancer, and identifies emphysema (84).

It is essential for distinguishing COPD from asthma, bronchiectasis, and congestive heart failure. To do so, the Bronchodilator Reversibility Test is a valuable diagnostic tool. A short-acting β2-adrenergic receptor agonist (SABA) is administered to widen the lung passages and relieve obstruction. Consequently, FEV1 levels are expected to rise. If not, the diagnosis is more likely to be COPD (1).
Questionnaires related to COPD assessment tests and exacerbation history help evaluate symptom burden, classify the disease further and guide therapy (85).

1.1.8. Classification

COPD is staged based on the severity of airflow limitation, symptoms, and exacerbation risk, primarily guided by the GOLD classification. Traditional spirometric staging (GOLD 1–4) categorizes disease progression using post-bronchodilator $FEV_1/FVC < 0.70$ and FEV_1 (% predicted). Reduced FEV_1 classifies disease severity (**Table 1**) (1).

Classification of airflow obstruction severity in COPD (based on post-bronchodilatator FEV_1)		
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very Severe	$FEV_1 < 30\%$ predicted
In patients with $FEV_1/FVC < 0.70$		

Table 1 *GOLD Grades and airflow obstruction severity (data sourced from GOLD report 2024 (1))*

To evaluate symptom burden and exacerbation history, the updated GOLD ABE assessment uses tools to refine management strategies. Among these, the COPD Assessment Test (CAT) and the Medical Research Council Classification (mMRC) are widely utilized (**Figure 1**) (1).

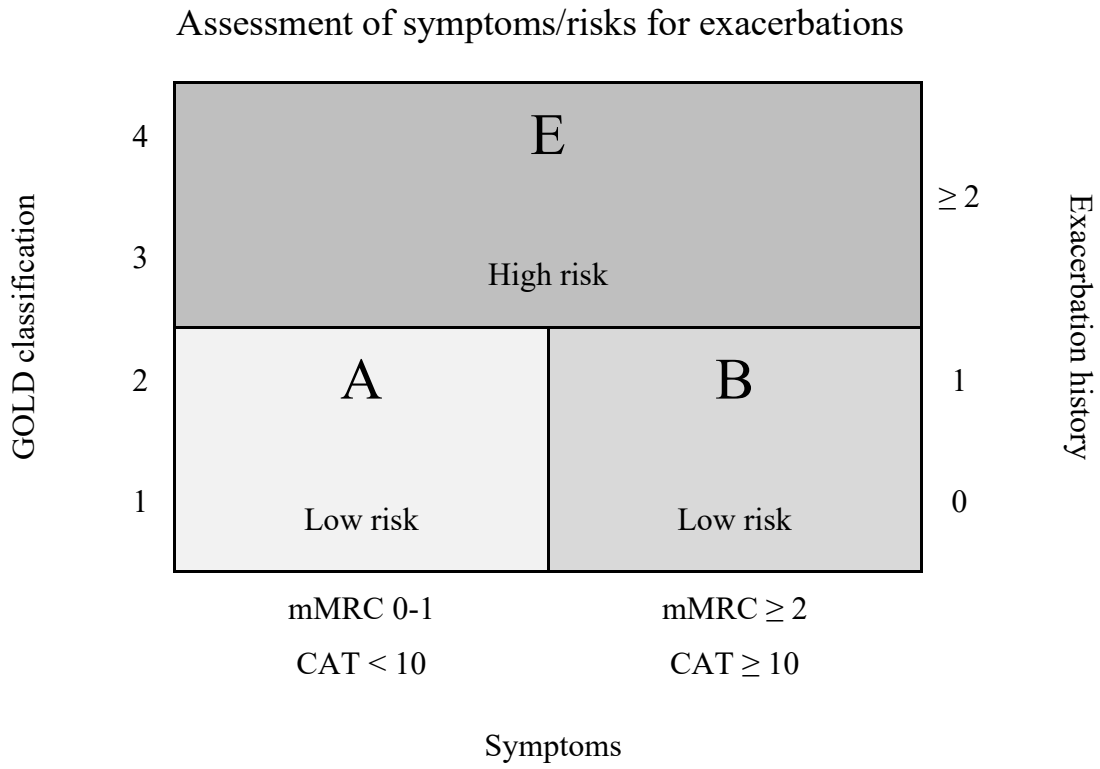

Figure 1 *The ABE assessment tool of GOLD guidelines (data sourced from GOLD report 2024 (1))*

1.1.9. Treatment

Therapeutic interventions are designed to alleviate symptoms and reduce the frequency of exacerbations (1).

Non-Pharmacological Treatments

Non-pharmacological interventions serve to complement pharmacologic therapies in the improvement of symptoms, functional capacity, and overall quality of life (86).

A fundamental component of COPD management entails smoking cessation and the avoidance of other deleterious inhaled substances. This approach has been identified as the most efficacious intervention to decelerate the progression of lung function decline (87).

In addition to that, regular physical activity is strongly recommended to enhance quality of life and mitigate systemic risk factors associated with comorbid conditions (88). Pulmonary rehabilitation employs a multidisciplinary approach that encompasses supervised exercise training, respiratory exercises, nutritional counseling, disease education, and psychological support. These interventions are designed to address physical deconditioning, enhance mobility, and empower patients with the knowledge necessary to effectively manage their condition across various stages of disease progression (89).

Preventive strategies, such as vaccinations, are also essential in reducing the risk of exacerbation and infection-related complications. It is imperative that patients receive routine immunizations against influenza, pneumococcus, and the novel strain of severe acute respiratory syndrome (SARS-CoV-2) (90).

Pharmacotherapies

Pharmacotherapy occupies a pivotal position in the management of COPD. Pharmacological interventions are primarily categorized into three classifications: bronchodilators, anti-inflammatory agents, and adjunctive therapies that target specific disease phenotypes (91). The GOLD report emphasizes an individualized approach to pharmacological management, integrating both symptom burden and future risk of exacerbations into a composite GOLD ABE assessment (1).

In patients with low symptoms and low exacerbation risk (Group A), initial therapy typically includes a short-acting bronchodilator (SABA or short-acting muscarinic antagonist), or a

single long-acting bronchodilator, including long-acting β2-agonist (LABA) or long-acting muscarinic antagonist (LAMA), for persistent symptoms.

For more symptomatic patients or those with a history of one exacerbation in the past year (Group B and E), combination LABA/LAMA therapy is increasingly favored over LABA/ICS due to better efficacy and lower risks of pneumonia associated with inhaled corticosteroids (ICS) (1).

Patients with high symptom burden and frequent exacerbations (Group E) are often initiated on LABA/LAMA dual therapy, with escalation to triple therapy (LABA/LAMA/ICS) if eosinophil counts are elevated (>300 cells/μL) or exacerbations persist. Additional agents such as phosphodiesterase-4 (PDE-4) inhibitors or macrolide antibiotics may be considered in select Group E patients with chronic bronchitis or recurrent exacerbations despite optimized inhaled therapy (1).

The treatment regimen must be regularly reassessed and adjusted to the patient's needs (92). In instances where patients within risk group E demonstrate no improvement in symptoms, the administration of Long-Term Oxygen Therapy and Non-Invasive Ventilation may be contemplated. Long Term Oxygen Therapy is indicated when patients have been receiving oxygen by nasogastric tube for at least 18 hours and resting arterial oxygen partial pressure is <55 mmHg (1).

Treatment decisions are further tailored based on comorbidities, side effect profiles, and patient preference, underscoring the importance of a personalized approach in COPD pharmacotherapy (93).

Interventional management

Surgical and interventional therapies are reserved for patients with severe or very severe disease who remain symptomatic despite optimal medical management (1).

The Lung Volume Reduction Surgery involves the excision of damaged lung tissue, particularly in cases of upper-lobe-predominant emphysema, with the objective of enhancing breathing mechanics. For patients with heterogeneous emphysema, the Endobronchial Valve Therapy in diseased lung segments is more beneficial. A range of surgical interventions exist for the treatment of bullae when conventional therapeutic interventions have been unsuccessful (1).

Lastly, lung transplantation is a treatment option for patients with end-stage COPD. However, this procedure is limited by the availability of donors and the necessity of long-term immunosuppression (1).

Despite the diverse array of treatment options currently available, no therapeutic interventions have been proven effective in halting the progression of COPD (94).
The utilization of bronchodilators and glucocorticoids are both associated with significant adverse effects. The commonly reported side effects of β2-receptor agonists include tachycardia, muscle tremors, and metabolic disturbances (95). Anticholinergics have been observed to induce a range of adverse effects, including dry mouth, blurred vision, urinary retention, postural hypotension, cognitive impairment, and cardiac arrhythmias (96).
In addition, prolonged glucocorticoid use has been demonstrated to lead to corticosteroid resistance and to induce immunosuppression, which can lead to an increased susceptibility to and exacerbation of infections. Furthermore, this use has been associated with the development of hyperglycemia, osteoporosis, and psychiatric disorders (97). Also the utilization of medications such as PDE-4 inhibitors, adenosine receptor inhibitors, and cytokine inhibitors has been constrained due to their adverse effects, inefficiency, resistance, and clinical failure (98).

Consequently, there is an imperative for the development of alternative therapeutic strategies to address the limitations of current therapeutic modalities and to block the progression of COPD. Among these emerging targets, sirtuins (SIRTs) are of particular interest, given their potential roles as modulators of the key pathogenic pathways associated with COPD.

1.2. SIRTs Family

1.2.1. Definition and Overview

Sirtuins are a family of evolutionarily conserved, NAD^+-dependent enzymes found throughout the animal kingdom and beyond and play a pivotal role in regulating essential cellular processes (99). They function primarily as histone and protein deacetylases and belong to the class III histone deacetylase family (HDAC III). They are distinguished from HDAC classes I and II by their dependence on NAD^+ rather than zinc as a cofactor (100).

Sirtuins are homologous to the Saccharomyces cerevisiae silent information regulator 2 protein, also known as the silent information regulator 2 (101).

In mammals, the sirtuin family comprises seven members, SIRT1 through SIRT7, which differ in subcellular localization, enzymatic activity, and molecular targets. They are widely expressed across various tissues and regulate diverse physiological functions by catalyzing the removal of acetyl groups from specific lysine residues on target proteins (53).

Sirtuins play a role in a variety of biological processes, including gene expression, cellular metabolism, DNA repair, inflammation, and stress responses (102).

1.2.2. Evolution

The sirtuin family was first identified in yeast in 1979 during studies on mating type (MAT) loci. A mutation in the MAT locus led to the discovery of the silent information regulator 2 protein, which was later shown to play a key role in transcriptional silencing and aging (55). Four additional sirtuin-related genes, named HST1–4, were subsequently identified in yeast, thereby expanding the known repertoire of this protein family (54).
Homologs of silent information regulator 2 were soon discovered in other eukaryotic organisms, including nematodes, fruit flies, and mammals (56).

SIRT1 was the first mammalian homolog to be characterized (53). While seven canonical sirtuins are recognized in humans, ongoing research continues to explore the possibility of additional isoforms or variants. In early 2023, Opazo et al. identified a novel mitochondrial sirtuin variant, termed sirtuin 3.2, in cartilaginous fish (57).

1.2.3. Localization, Structure, and Mode of Action

SIRT1

SIRT1 is primarily located in the nucleus. However, under specific conditions, it can shuttle to the cytoplasm, allowing it to regulate cytoplasmic processes (103).

SIRT1 has a large catalytic core domain that binds to NAD^+, which is essential for its deacetylase activity. This domain is highly conserved among sirtuins, enabling SIRT1 to remove acetyl groups from lysine residues on its target proteins, including p53, NF-κB, and Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α (69). In addition to the catalytic core, SIRT1 has extended N- and C-terminal regulatory regions that facilitate

substrate recruitment, cofactor interaction, and subcellular localization. Notably, SIRT1 contains nuclear localization signals and nuclear export signals, which enable it to shuttle dynamically between the nucleus and the cytoplasm (104).

SIRT1 is an NAD^+-dependent deacetylase that plays an important role in metabolic regulation and stress response. Its structural regulatory regions enable SIRT1 to influence gene expression, mitochondrial function, and inflammatory signaling (105). For instance, SIRT1 deacetylates forkhead box transcription factors (FOXO) family members and interacts with chromatin-modifying complexes, thereby effecting DNA repair, cell cycle arrest, and longevity pathways (69). These regulatory functions establish SIRT1 as a central mediator of cellular adaptation and stress resistance (106).

SIRT2

SIRT2 is predominantly found in the cytoplasm (107). However, during specific phases of the cell cycle, particularly the G2/M transition, SIRT2 can localize to the nucleus (108).

SIRT2 contains a catalytic core domain that is analogous to those of other sirtuins. It has been demonstrated to bind NAD^+ and to mediate deacetylase activity. The core is characterized by its high degree of specialization in targeting cytoplasmic substrates, with a particular emphasis on α-tubulin (109). In contrast to SIRT1, SIRT2 exhibits smaller regulatory regions (110).

In addition to its NAD^+-dependent deacetylase activity, SIRT2 has been shown to possess adenosine diphosphate (ADP)-ribosyltransferase activity. This enables it to regulate protein function beyond acetylation status (111).

SIRT2 plays a pivotal role in the regulation of the cell cycle and the dynamics of microtubules through the deacetylation of α-tubulin (112). SIRT2 also modulates inflammatory signaling, particularly via interaction with the NF-κB pathway (113). It has been implicated in macrophage polarization, where it may promote an anti-inflammatory or pro-inflammatory phenotype depending on the context (114). Furthermore, SIRT2 has been demonstrated to regulate critical metabolic enzymes, including glyceraldehyde-3-phosphate dehydrogenase (GAPDH), thereby impacting glycolytic flux and redox balance within the cell (115).

SIRT3

SIRT3 is localized to mitochondria, where it maintains mitochondrial function and energy metabolism (116). In addition to its primary mitochondrial location, SIRT3 is also found in the nucleus under normal growth conditions. However, under conditions of DNA damage induced by etoposide and ultraviolet irradiation, SIRT3 redistributes from the nucleus to the mitochondria (117).

The structure of SIRT3 is optimized for mitochondrial function, featuring a catalytic core domain that binds NAD^+ and exhibits robust deacetylase activity. This domain is highly efficient at deacetylating mitochondrial proteins, such as superoxide dismutase 2 (SOD2) (118). Unlike nuclear sirtuins, SIRT3 lacks extended regulatory regions (119).

As a mitochondrial NAD^+-dependent deacetylase, SIRT3 plays a pivotal role in maintaining redox homeostasis, regulating mitochondrial function, and influencing cellular metabolism (120). The most well-characterized target of this process is SOD2, where SIRT3-mediated deacetylation has been shown to increase SOD2 efficiency in neutralizing mitochondrial superoxide radicals (121). Furthermore, SIRT3 activates isocitrate dehydrogenase 2 (IDH2), which in turn promotes NADPH generation and supports glutathione recycling under conditions of oxidative stress (122).
In addition to its role in ROS detoxification, SIRT3 modulates components of the electron transport chain, including complex I subunits. Through these interactions, SIRT3 enhances mitochondrial efficiency and reduces the accumulation of ROS (123).
SIRT3 has also been demonstrated to be implicated in the processes of fatty acid oxidation and ketogenesis, particularly in states of fasting or metabolic stress (124).

SIRT4

SIRT4 resides in the mitochondrial matrix (125).

It possesses a catalytic core domain that binds NAD^+, but its deacetylase activity is relatively weak compared to other sirtuins. Instead, SIRT4 exhibits ADP-ribosyltransferase activity, enabling it to modify target proteins through ADP-ribosylation (126).

Given its structural characteristics, SIRT4 has been shown to regulate mitochondrial metabolism and insulin secretion (127). By ADP-ribosylating and thereby inhibiting glutamate dehydrogenase (GDH), it has been demonstrated to suppress amino acid-stimulated insulin release from pancreatic β-cells in response to amino acids (128). SIRT4

has also been shown to modulate fatty acid oxidation via Peroxisome Proliferator-Activated Receptor-α (PPAR-α) activity and mitochondrial gene expression by interacting with tricarboxylic acid cycle components (129).
Collectively, these functions establish SIRT4 as a metabolic sensor that integrates nutrient availability with mitochondrial function and insulin homeostasis (130).

SIRT5

SIRT5 is also found in the mitochondrial matrix. However, it can also be found in the cytoplasm and nucleus. It has been demonstrated that, among all sirtuin isoforms, this is the most dynamic (131).

In terms of structural features, SIRT5 was observed to exhibit a comparable overall domain organization and fold to that of SIRT1, SIRT2, and SIRT3 (132).

SIRT5 is a distinctive sirtuin that governs lysine post-translational modifications that extend beyond acetylation. It possesses a catalytic core domain with demalonylase, desuccinylase, and deglycase activities, enabling it to remove malonyl, succinyl, and glutaryl groups from lysine residues on target proteins. In contrast to other sirtuins, SIRT5 displays only modest deacetylase activity (133). It acts on key metabolic enzymes, such as carbamoyl phosphate synthetase 1, GAPDH, and cytochrome c. By modifying these targets, SIRT5 influences the activity of the urea cycle, glycolysis, and redox homeostasis (134).

SIRT6

SIRT6 is a nuclear sirtuin. It is distinguished by its dual enzymatic activities, encompassing deacetylase and mono-ADP-ribosyltransferase functions (135).

These activities are facilitated by a specialized NAD^+ binding pocket, a structural element that contributes to its unique biological functions. In addition to its catalytic core, SIRT6 contains a distinctive C-terminal helix that enhances its DNA-binding affinity and chromatin remodeling capacity. This feature differentiates it from other sirtuins, such as SIRT1 and SIRT3, which rely more heavily on their conserved catalytic domains for deacetylase activity (136).

SIRT6 is considered a highly potent nuclear deacetylase and exhibits a high degree of binding to chromatin (137). It plays a key role in preserving genome stability and modulating inflammation by deacetylating histones, including histone H3 lysine 9 (H3K9) and H3 lysine

56 (H3K56) (138). It has been demonstrated to support efficient DNA repair, particularly in the context of oxidative DNA damage (139). SIRT6 has also been shown to suppress NF-κB signaling, thereby reducing pro-inflammatory cytokine production (140).
In addition, SIRT6 has been identified to modulate glucose metabolism through its interaction with hypoxia-inducible factor (HIF1)α and PPARγ, thereby impacting glycolysis and lipid homeostasis (141).

SIRT7

SIRT7 is uniquely localized to the nucleolus. It contains a nucleolar localization signal and a variable C-terminus that helps it interact with ribonucleic acid (RNA) polymerase I and other nucleolar proteins (142).

SIRT7 possesses a catalytic core domain with weak deacetylase activity but strong capabilities in ribosomal RNA processing and ribosome biogenesis. Its catalytic domain is connected to a zinc-binding domain, forming a large pocket adjacent to the primary catalytic site. This secondary pocket is thought to support additional enzymatic activities beyond classical deacetylation (143).

SIRT7 has been shown to display not only deacetylase activity, but also mono-ADP-ribosyltransferase, desuccinylase, debutyrylase, defatty-acylase, and decrotonylase functions (144). Unlike other sirtuins, SIRT7's enzymatic activity is tailored for interactions with nucleolar components rather than histones or metabolic enzymes. It plays a crucial role in ribosome biogenesis and RNA transcription, where it interacts with the RNA polymerase I machinery, to regulate rRNA synthesis and translation capacity (145). Its role in mitochondrial-nucleolar crosstalk suggests that SIRT7 also influences mitochondrial protein synthesis and respiratory chain function, allowing it to regulate cellular growth and proliferation (143).

Recent findings suggest a potential role for SIRT7 in the DNA damage response and apoptosis regulation, particularly in situations of genotoxic stress (146).

	Localization	Enzymatic activity	Biological function
SIRT1	Nucleus, cytoplasm	Deacetylase	Inflammation, oxidative stress, cell cycle regulation and apoptosis, aging, DNA repair
SIRT2	Nucleus, cytoplasm	Deacetylase, ADP-ribosyltransferase	Cell cycle regulation, apoptosis, DNA repair, aging, metabolism, oxidative stress
SIRT3	Mitochondria	Deacetylase	Mitochondrial, metabolism, oxidative stress, energy production
SIRT4	Mitochondria	ADP-ribosyltransferase, lipoamidase, deacetylase	Insulin secretion, glucose homeostasis, oxidative stress
SIRT5	Mitochondria	Desuccinylase, demalonylase, deglutarylase, deacetylase	Oxidative stress, glycolysis, fatty acid oxidation, urea cycle cellular respiration
SIRT6	Nucleus	Deacetylase, mono-ADP-ribosyltransferase	Senescence and oxidative stress
SIRT7	Nucleolus	Deacetylase, desuccinylase	Ribosomal DNA transcription

Table 2 *Characteristics and Functions of the Mammalian Sirtuin Family (data sourced from Li et al. (2023) (147)*

Emerging evidence indicates that sirtuins function as molecular regulators of key pathophysiological mechanisms relevant to COPD. Depending on the isoform and cellular context, certain sirtuins exhibit anti-inflammatory, antioxidant, or mitochondrial-protective effects, positioning them as potential modulators of disease progression (148).

The subsequent sections will examine the potential contributions of sirtuins, if any, to the development and progression of COPD.

2. Aim of the Thesis

The objective of this narrative review is to provide a thorough and analytical overview of the most recent scientific advancements concerning the role of sirtuins in the pathophysiology of COPD.

Specifically, it examines the role of sirtuins in driving central pathological processes in COPD, encompassing persistent airway and systemic inflammation, excessive oxidative stress, and impaired mitochondrial function. These elements contribute to the progression and severity of the disease.

Despite accumulating evidence of their regulatory roles in cellular stress responses and aging-related pathways, the involvement of sirtuins in COPD remains underexplored and fragmented across disciplines. This work aims to address this knowledge gap by consolidating and interpreting the current findings.

Consequently, it evaluates the emerging potential of sirtuins as novel therapeutic targets. The thesis concludes with the proposal of a forward-looking perspective, namely that targeted modulation of sirtuin activity has the potential to pave the way for more personalized and effective COPD treatments. It calls for increased research investment and clinical consideration of sirtuin-centered approaches in respiratory medicine.

3. Methods

To obtain preliminary fundamental information, the scientific literature in print or online versions from the Medical University of Graz's library was consulted, in addition to the current guidelines of GOLD. A thorough review of the extant literature, encompassing studies, reviews, and meta-analyses, was conducted in both German and English to address the research question. These sources were retrieved from databases such as PubMed, ClinicalTrials.gov, and Google Scholar.
To conduct a more comprehensive analysis, publications from the last six years (2019-2025) were prioritized.

A total of 29 studies were conducted to investigate sirtuin expression, activity, or function in the context of COPD. The aforementioned studies employed a variety of methodologies, including the utilization of human clinical samples, and/or in vivo models, and/or in vitro systems. Out of a total of 29 experiments, 5 of them involved the use of human samples, 23 utilized mice, and 18 employed cell samples. In the selection process, priority was given to the most relevant to answering the research question.

A set of specific inclusion and exclusion criteria were applied to ensure the relevance and quality of the included studies. The selection of studies was based on the following criteria: an emphasis on sirtuins and a focus on COPD pathophysiology. Priority was given to articles that underwent a peer-review process, as well as to meta-analyses and systematic reviews. Publications that did not directly address the role of sirtuins in COPD or its pathological pathways or that lacked methodological clarity were excluded from the analysis.

Despite the comprehensive nature of this narrative review, which synthesizes extant knowledge, it is imperative to acknowledge its limitations. As a non-quantitative approach, it does not permit statistical comparisons or definitive conclusions about causal relationships between sirtuins and COPD. Furthermore, the subjective nature of narrative reviews may introduce potential biases in study selection and interpretation. Nevertheless, measures were implemented to mitigate such bias by prioritizing high-quality, frequently cited sources and by cross-referencing findings across studies.

The application of ethical considerations to this review was not directly pertinent due to the absence of human or animal data collection.

4. Sirtuins in COPD

In order to maintain a cohesive narrative, the extent to which SIRTs have been involved in the core mechanisms and pathways of COPD leading to significant abnormal cellular and molecular changes will be further examined in this section. Additionally, the intricate crosstalk among sirtuin family members and their interactions with key signaling pathways will be explored, culminating in an assessment of their functional role, whether as active drivers or modulatory participants, in COPD pathogenesis.

4.1. SIRTs Related Pathways

A variety of sirtuins modulate these pathways through both direct enzymatic actions and indirect mechanisms. Integration of the extant literature on sirtuin-pathway interactions provides a framework for understanding their potential roles as molecular regulators in the pathogenesis of COPD.

4.1.1. Inflammatory Signaling Pathways

NF-κB Signaling Pathway

The NF-κB signaling pathway plays a key role in mediating inflammation in COPD by regulating the expression of various pro-inflammatory cytokines, including TNF-α, IL-6, and IL-8. These cytokines contribute to persistent airway inflammation and structural damage. Under normal conditions, NF-κB remains inactive in the cytoplasm. Activation is often triggered by cigarette smoke or oxidative stress, allowing NF-κB dimers, primarily p65/p50, to translocate into the nucleus and initiate transcription of inflammatory genes (149).

In the lungs of people with COPD, this pathway is chronically active, particularly in alveolar macrophages and epithelial cells (150). This contributes to sustained inflammation, mucus hypersecretion, and alveolar destruction (151). SIRT1 acts as a protective factor by deacetylating the p65 subunit, which reduces its DNA-binding affinity and downstream inflammatory signaling. In COPD, downregulation of SIRT1 has been strongly associated with increased NF-κB activity and cytokine production (152).

As demonstrated by Ma et al. (2019), increased SIRT1 directly modulates NF-κB, specifically deacetylating its p65 subunit, thereby suppressing its transcriptional function. The researchers employed human macrophages, which were exposed to cigarette smoke extract (CSE) to mimic COPD-like inflammatory conditions. Concurrently, mice were subjected to cigarette smoke (CS) exposure to model disease progression in vivo. The expression levels of SIRT1 and NF-κB were subsequently evaluated through the implementation of Western blotting in both human macrophages and mouse lung tissues. Consequently, the SIRT1-mediated inhibition of NF-κB significantly reduces downstream inflammatory mediator production in response to CS (153).

Jin et al. (2022) demonstrated that interventions ameliorated inflammation and lung damage in a rat COPD model by activating SIRT1 and suppressing NF-κB signaling. The study's objective was to induce COPD in a total of 70 male rats over a period of 12 weeks. This was achieved by repeated exposure to CS. Following the conclusion of the intervention period, pulmonary function and lung histopathology were evaluated. Furthermore, the levels of components of the SIRT1/NF-κB signaling pathway were examined in lung tissue. The augmentation of SIRT1 expression has been demonstrated to result in a decrease of NF-κBp65 and its acetylated form, consequently leading to a reduction in pro-inflammatory cytokines and an enhancement in anti-inflammatory IL-10 (154).

Additionally, SIRT2 modulates NF-κB by directly by deacetylating p65, thereby reducing the activity of this key inflammatory pathway (113).

As demonstrated by Liu et al. (2021), exposure to particulate matter (PM), a harmful and common air pollutant in developing countries, has been shown to suppress SIRT2 expression and activity in bronchial tissues. This suppression has been found to promote dual phosphorylation and acetylation of the NF-κB subunit p65. The study was conducted in vivo using wild-type and SIRT2 knockout mice exposed to ambient $PM_{2.5}$ via inhalation for 28 days to model airway inflammation. Notably, the experimental design focused on $PM_{2.5}$-induced inflammatory responses mimics key features of obstructive airway disease. The resulting hyperactivation of NF-κB signaling has been observed to trigger airway inflammation, mucus hypersecretion, and bronchial hyperresponsiveness (155).

NLRP3 Inflammasome Pathway

The NLRP3 inflammasome plays a pivotal role in the mediation of sterile inflammation in COPD (156). The activation of this receptor is initiated by exposure to CS, PM, and mitochondrial DAMPs. Following the initial priming by NF-κB signaling, the NLRP3 inflammasome is subsequently activated by oxidative stress or lysosomal disruption (157). This results in the activation of caspase-1 and the subsequent release of the pro-inflammatory cytokines IL-1β and IL-18 which induce persistent airway inflammation, epithelial injury, and systemic immune activation (158).

Studies suggest that NLRP3 inflammasome activation contributes to pulmonary inflammation, tissue remodeling, and metabolic reprogramming, reinforcing its role in disease progression (159). SIRT1 has been shown to suppress NLRP3 inflammasome priming by inhibiting the NF-κB-dependent expression of NLRP3 (160).

The study by Yang et al. (2024) examined the association between SIRT1 deficiency and NLRP3 inflammasome-driven inflammation in conditions analogous to COPD. The researchers employed rat macrophage cells exposed to CSE as an in vitro model of COPD. The researchers found that CSE exposure led to a decrease in SIRT1 expression, an increase in M1 macrophage polarization, and an elevated release of pro-inflammatory cytokines. Mechanistically, SIRT1 expression has been shown to suppress activation of the NLRP3 inflammasome pathway, leading to a reduction in NLRP3 expression (161).

Tian et al. (2021) identified histidine as a protective agent against induced COPD-like lung inflammation and emphysema by suppressing NLRP3 inflammasome activation. The inhibition of the NLRP3 inflammasome has been demonstrated to be SIRT1-mediated. To create an in vivo mouse model of COPD, female mice were utilized. The subjects were exposed to repeated intranasal administration of elastase and lipopolysaccharide. Concurrently, in vitro experiments were conducted with mouse alveolar macrophages (162).

MAPK Signaling Pathway

The mitogen-activated protein kinase (MAPK) pathway, specifically the p38 MAPK and c-Jun-N-terminal kinase branches, has been demonstrated to play a substantial role in the process of stress-induced inflammation and epithelial cell apoptosis in the context of COPD (163). It has been shown to result in increased expression of inflammatory mediators. The

persistent stress leads to chronic tissue damage and impaired repair mechanisms (164). SIRT1 has emerged as an important modulator of MAPK signaling (165).

Lai et al. (2019) demonstrated that PM exposure reduces SIRT1 expression in human bronchial epithelial cells and mouse lungs. Human bronchial epithelial cells were exposed to standardized PM to assess airway inflammatory responses, while male mice received intratracheal PM instillations to model PM-induced lung inflammation. As a result, it was shown that reduced SIRT1 lead to airway inflammation which was mediated partly through MAPK signaling pathways (166).

4.1.2. Oxidative Stress and Antioxidant Defense Pathways

Nrf2/HO-1 Signaling Pathway

The Nrf2/Keap1/HO-1 pathway functions as a central defense mechanism against oxidative stress in COPD (167). Under normal conditions, nuclear factor erythroid 2-related factor 2 (Nrf2) is retained in the cytoplasm and is negatively regulated by Kelch-like ECH-associated protein 1 (Keap1). Upon exposure to ROS, Nrf2 translocates to the nucleus and activates cytoprotective and antioxidant genes, which have been demonstrated to aid in the neutralization of ROS (168).
Research has already revealed that Nrf2-knockout mice exhibited indications of inflammation in the bronchoalveolar lavage following exposure to CS (169).

Kawasaki et al. (2021) demonstrated that impaired nuclear translocation of Nrf2 drives COPD pathogenesis by suppressing SIRT1 expression, resulting in heightened lung inflammation and apoptosis in mouse models of COPD, where emphysema was induced by intratracheal administration of porcine pancreatic elastase. It is imperative to note that the restoration of Nrf2 nuclear shuttling led to the attenuation of SIRT1 reduction and the protection against emphysema (170).

Mitochondrial ROS Detoxification and Ferroptosis Regulation

Mitochondria have been identified as a significant source of ROS, particularly in alveolar epithelial cells and macrophages exposed to chronic CS (171). One of the major pathways is the SIRT3-MnSOD axis, which plays a critical role in detoxifying mitochondrial superoxide and maintaining redox homeostasis.

Among the sirtuins, SIRT3 has been shown to deacetylate and activate manganese superoxide dismutase (MnSOD), thereby enhancing its capacity to convert superoxide radicals into hydrogen peroxide (172).

Zhang et al. (2020) demonstrated that the downregulation of SIRT3 significantly decreased the activity of MnSOD, thereby exacerbating oxidative damage and cell injury in vivo and in vitro. The COPD rat model was induced by chronic CS exposure and intratracheal lipopolysaccharide instillation, while human bronchial epithelial cells were treated with CSE. The restoration of SIRT3 led to the preservation of MnSOD and a reduction in oxidative stress, confirming its role in mitochondrial antioxidant defense (173).

Furthermore, findings highlight the role of SIRT3 in modulating ferroptosis, a type of regulated cell death associated with lipid peroxidation and iron overload driven by ROS (174).

A study by Zi et al. (2023) demonstrated that CSE activates inducible nitric oxide synthase (iNOS), promoting ferroptosis in human bronchial epithelial cells. SIRT3 inhibits iNOS activity; however, CSE-induced ROS suppresses the upstream regulator Nrf-2, which downregulates SIRT3 expression. The Nrf-2/SIRT3-iNOS-ferroptosis pathway significantly contributes to bronchial epithelial injury and may play a role in COPD progression (175). Also, SIRT4 was found to be involved in ferroptosis (176).

Li et al. (2023) revealed that CSE downregulates SIRT4 in lung tissues and alveolar epithelial cells, which drives ferroptosis. Female mice were exposed to CS for a period of six months. Concurrently, human alveolar epithelial cells were exposed to CSE to investigate the underlying cellular responses. The researchers showed that the restoration of SIRT4 inhibit ferroptosis and alleviate CSE-induced lung damage (176).

Post-Translational Redox Regulation

Beyond the established antioxidant pathways, emerging evidence has underscored the significance of post-translational modifications (PTMs) in redox regulation, specifically PTMs involving lysine residues, such as malonylation and succinylation (177).

A lack of research has persisted, with no studies examining these modifications in COPD and SIRT5 in the past six years.

However, in the context of sepsis-induced lung inflammation, Zhang et al. (2024) have demonstrated that SIRT5 desuccinylates tank-binding kinase 1 (TBK1) in human and mouse

macrophage cell lines. A decrease in SIRT5 levels has been demonstrated to enhance TBK1 succinylation, consequently diminishing the synthesis of inflammatory cytokines (178). Additional studies are required to establish a direct correlation between the condition in question and COPD.

4.1.3. Mitochondrial Dysfunction and Bioenergetics

SIRT1-PGC-1α Signaling Pathway

SIRT1 deacetylates and activates peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), which enhances mitochondrial function (179). In COPD, CS exposure reduces SIRT1 levels, which impairs PGC-1α activity. This leads to lower mitochondrial density and bioenergetic capacity (147).

Zhang et al. (2021) showed that exposure to $PM_{2.5}$ downregulates the expression of the proteins SIRT1 and PGC-1α in male rats. The study investigated PM-induced lung injury, airway inflammation and mitochondrial damage, all pathological features that may overlap with COPD (180).

Also, Ren et al. (2025) demonstrated that activating the AMPK/SIRT1/PGC-1α axis can ameliorate cellular senescence and COPD-like symptoms. In this study, human bronchial epithelial cells were exposed to CSE to model cellular senescence. In addition, male mice were exposed to CS for 24 weeks to establish a direct experimental model of COPD. In COPD mice, SIRT1 and its downstream effector, PGC-1α, were upregulated. Upregulation of these proteins enhanced mitochondrial biogenesis and metabolism, reducing ROS levels. This suppressed oxidative stress and senescence markers, ultimately reducing lung damage and inflammation (181).

SIRT3-SOD2-Axis

The SIRT3-SOD2 axis plays a critical role in mitochondrial redox homeostasis. SIRT3 deacetylates and activates SOD2, the key antioxidant enzyme that neutralizes superoxide radicals within mitochondria (182).

Liao et al. (2025) showed that exposure to CS induces a significant oxidative imbalance and cellular senescence, as indicated by elevated mitochondrial ROS, acetylated SOD2, and downregulated SIRT3 expression as a result. The study employed a multi-level experimental approach, integrating human lung tissue analysis from 21 patients with and without COPD,

in vivo mouse models, and human bronchial epithelial cells, to investigate the role of SIRT3 and hydrogen sulfide in CS–induced lung damage relevant to COPD. Accordingly, it emphasizes the pivotal role of the SIRT3–SOD2 axis in mitigating oxidative stress and senescence (183).

Cell energy metabolism

A substantial body of research has demonstrated the presence of mitochondrial dysfunction in patients diagnosed with COPD (184).

Wan et al. (2024) investigated the role of Krüppel-like factor 6 in CSE-induced mitochondrial dysfunction. The authors employed an in vitro COPD model; whereby human bronchial epithelial cells were exposed to CSE. The assessment of cell viability, inflammation, and mitochondrial parameters was conducted, including ATP production, mitochondrial membrane potential, and Complex I activity. The researchers discovered that CSE increased the expression of Krüppel-like factor 6, which directly interacted with the SIRT4 promoter, thereby repressing its transcription. This downregulation of SIRT4 has been associated with severe mitochondrial dysfunction, characterized by reduced ATP levels and decreased Complex I activity (185).

Mitochondrial Apoptotic Signaling and Autophagy

Mitochondria-mediated apoptosis is a major contributor to alveolar cell death and tissue destruction in COPD (186). Mitochondrial outer membrane permeabilization leads to the release of cytochrome c. SIRT3 influences this process, which activates the caspase cascade. Caspase activation and the loss of protective mechanisms results in increased apoptosis and alveolar wall thinning in emphysematous lungs (187).

Ishimori et al. (2025) identified that SIRT3 deficiency in the lungs of patients with COPD and in human bronchial epithelial cells exposed to CS triggers caspase-3-mediated apoptosis, thereby driving emphysema pathology. Also, a COPD mouse model was established by means of intratracheal elastase instillation, followed by repeated lipopolysaccharide instillations. Studies were conducted in SIRT3 knockout and SIRT3-overexpressing transgenic mice. SIRT3 knockout mice exhibited significantly elevated levels of activated caspase-3 in lung tissues. These findings indicate that the loss of SIRT3 promotes apoptotic

cell death via the caspase-3 pathway, directly contributing to the development of COPD-like lung structural damage (188).
Additionally, it is known that SIRT1 deacetylates FOXO3 and p53, limiting their pro-apoptotic effects (189).

The researchers Wang et al. (2024) demonstrate that elevated SIRT1 levels inhibit CSE-induced mitophagy, the mitochondrial autophagy, and reduce apoptosis in human bronchial epithelial cells and female mice (190).

In COPD mice, Jiang et al. (2022) identified that SIRT1 deacetylates FOXO3, thereby activating mitophagy and protecting against CS-induced mitochondrial damage and cellular senescence. SIRT1 deficiency has been demonstrated to impair this process, resulting in the exacerbation of lung pathology (191).

4.1.4. Cellular Senescence and Aging Pathways

Cell Cycle Arrest Pathways

The $p16^{INK4}$/RB and p53/$p21^{CIP1}$ pathways are central regulators of cellular senescence (192). In the context of numerous age-related diseases, including COPD, these pathways have been demonstrated to induce growth arrest in response to DNA damage, oxidative stress, and inflammatory signals (193). Over-expression of $p21^{CIP1}$ and p53 is capable of inducing bronchial club cell senescence (194).
SIRT1 has been implicated in suppressing these pathways (192).

As Bateman et al. (2023) described, SIRT1 deacetylates p53, reduces the transcription of $p21^{CIP1}$ and modulates retinoblastoma acetylation, thereby indirectly influencing the $p16^{INK4}$ pathway. Reduced SIRT1 levels in COPD correlate with increased $p16^{INK4A}$ and $p21^{CIP1}$ expression in airway epithelium, suggesting that loss of sirtuin-mediated cell cycle control contributes to premature senescence and tissue degeneration (195).

DNA Damage Response and Repair Pathways

Chronic exposure to CS and environmental toxins generates persistent DNA lesions, particularly double-strand breaks, which activate the DNA damage response (196).

According to Yan et al. (2021), the persistent activation of the DNA damage repair (DDR) response results in the suppression of SIRT1 deacetylase activity. This downregulation

enhances the transcriptional activity of p53, which in turn directly promotes the acceleration of cellular senescence. The research combines in vitro models, including human diploid and mouse embryonic fibroblast cells subjected to stress-induced premature senescence, with in vivo mouse models on premature aging. As a result, the researchers identified the DDR-SIRT1-p53 as a key molecular link driving senescence (197), which in turn overlaps with the pathology of COPD.

Senescence-Associated Secretory Phenotype (SASP)

The term SASP is used to collectively refer to the various pro-inflammatory cytokines, chemokines, growth factors, and matrix-degrading enzymes that are secreted by senescent cells. The accumulation of senescent cells in the lungs of patients with COPD is a consequence of chronic exposure to environmental insults, which further perpetuates chronic inflammation, extracellular matrix degradation, and tissue remodeling in COPD (198). The NF-κB and NLRP3 inflammasome activation are the primary regulatory mechanisms involved in this process, which is known to amplify the SASP response (199).
SASP expression is influenced by SIRT1 and SIRT6, which suppress NF-κB and p38 MAPK activation, both upstream inducers of SASP gene expression (200).

Zeng et al. (2022) demonstrated that exposure to CS leads to cellular senescence and the secretion of SASP in airway epithelium, a process that is facilitated by the suppression of SIRT1 via the action of miR-34a. Human bronchial epithelial cells were exposed to CSE to model CSE-induced cellular senescence. It showed that reduced SIRT1 deacetylates NF-κB less efficiently, leading to hyperacetylated, transcriptionally active NF-κB that drives pro-inflammatory SASP expression (201).

Baker et al. (2019) identified that the suppression of SIRT1 in COPD results in the modulation of SASP signaling, consequently influencing the progression of cellular senescence. In order to identify this link in vitro experiments were performed using primary small airway and human bronchial epithelial cells, where cellular senescence was induced by oxidative stress (202).

Regulation of MiRNAs

Micro-RNAs (miRNA) are a class of small noncoding, regulatory RNAs that have been shown to be the predominant epigenetic mechanism associated with the aging process. In

response to CS, studies have demonstrated that expression of miRNAs is dysregulated in COPD, with some miRNAs exhibiting increased expression and others decreased expression (203).

Baker et al. (2019) demonstrated that the restoration of SIRT1 through the inhibition of miR-570 reverses cellular senescence. The study utilized human clinical samples, including lung tissue, sputum, and primary small airway epithelial cells, from nonsmokers, smokers without COPD, and patients with COPD across all GOLD stages. The authors demonstrate that SIRT1 is downregulated in COPD airways and identify miR-570-3p as a direct post-transcriptional repressor of SIRT1. This work provides direct evidence that SIRT1 suppression by miR-570-3p contributes to airway epithelial dysfunction in human COPD (202).

Zeng and Zeng (2021) identified that oxidative stress upregulates miR-494-3p via the p38 MAPK-c-Myc pathway, which leads to suppressed SIRT3 expression in small airway epithelial cells. This downregulation correlates with increased senescence markers and elevated SASP proteins. Inhibiting miR-494-3p has been shown to reduce cellular senescence and inflammatory signaling (204).

In their 2022 study, Wu et al. employed a multifaceted approach, encompassing the use of human clinical samples, in vivo mouse models, and in vitro cell culture, to facilitate a comprehensive investigation. A total of 60 patients were included in the study, with the sample comprising never smokers, smokers without COPD, and smokers with COPD. This approach was adopted to ensure the study's strong clinical relevance. Concurrently, a mouse model of COPD was established by subjecting mice to CS for a period of 16 weeks. Complementary in vitro experiments employed mouse lung epithelial cells exposed to CSE. The researchers documented elevated levels of miRNA-125a-5p in lung tissues from smokers with and without COPD. These levels correlated with the severity of cellular senescence and reduced lung function. In both cells and mice, exposed to CS, elevated levels of miRNA-125a-5p have been observed to downregulate SIRT1 expression. This suppression has been demonstrated to initiate cellular senescence, the secretion of SASP, and the development of emphysema. Notably, the restoration of miR-125a-5p expression and the re-establishment of SIRT1 led to the reverse effects. These findings serve to substantiate the notion that the miR-125a-5p/Sp1/SIRT1/HIF-1α axis functions as a pivotal pathogenic mechanism in the context of smoke-induced COPD (205).

Another study by Shen et al. (2024) reported that male mice exposed to CS for 8 weeks exhibited a significant increase in miR-132 levels in lung tissues and bronchoalveolar lavage fluid. Notably, the miR-132 knockout mice exhibited a restoration of SIRT1 and downstream FOXO1 expression, which was accompanied by a significant improvement in lung function, preservation of tissue morphology, and reduction in cellular apoptosis. The study confirmed SIRT1 as a direct target of miR-132, thereby establishing that the inhibition of miR-132 attenuates the pathogenesis of COPD primarily through the reactivation of the SIRT1/FOXO1 axis (206).

PI3K/AKT/mTOR Signaling

The PI3K/AKT/mTOR pathway is a key regulator of cell growth and senescence. It includes three core components: Phosphoinositide 3-kinase (PI3K), which initiates signaling; protein kinase B (AKT) and mammalian target of rapamycin (mTOR), which subsequently inhibit SIRT1 and results in cellular senescence (78). Under chronic oxidative stress, this pathway is getting activated, contributing to decline in the messenger RNA (mRNA) expression of SIRT1 and SIRT6 and accelerated cellular senescence, which is marked by increased expression of SASP (207).

Korytina et al. (2023) identified significant genetic associations between SIRT1/3/6 polymorphisms and COPD risk, thereby revealing their mechanistic links to PI3K/AKT/mTOR dysregulation. This human genetic association study is focused on the investigation of COPD susceptibility in a Tatar population. The study encompassed 621 COPD patients and 624 control subjects. The researchers conducted an analysis of single nucleotide polymorphisms in genes associated with Sirtuins 1, 3, and 6, as well as the PI3K/AKT/mTOR pathway. The SIRT1 variant has been demonstrated to accelerate lung function decline by disrupting PI3K/AKT/mTOR signaling and NF-κB regulation. SIRT3 variants have been shown increased mitochondrial dysfunction and strong epistasis with PI3K subunit, resulting in the onset of oxidative stress and cellular damage. A correlation has been observed between reduced SIRT6 and increased susceptibility to COPD, which has been attributed to impaired DNA repair, NF-κB dysregulation, and autophagy failure. These factors, when synergizing with PI3K pathway genes, have been shown to amplify senescence. Polygenic analysis has confirmed the existence of functional crosstalk between sirtuins and PI3K/AKT/mTOR components. This finding positions the sirtuin-PI3K/AKT/mTOR axis as a significant regulator of COPD pathology (208).

4.1.5. Apoptosis

Intrinsic Apoptotic Pathway

The p53-Bax/Bcl-2 axis regulates the intrinsic mitochondrial apoptotic pathway, which is strongly activated in COPD due to DNA damage and oxidative stress. Upon activation, p53 promotes transcription of pro-apoptotic Bcl-2-Associated X Protein (Bax), which triggers cytochrome c release and caspase activation. In contrast, the anti-apoptotic Bcl-2, which is decreased in lungs of COPD patients, inhibits this process (209). The Bax/Bcl-2 ratio is a critical determinant of the apoptotic pathway (210).

Zeng et al. (2022) showed that SIRT1 upregulation through flavonoids leads to p53 deacetylation and downregulation. Suppressing p53 signaling increased the anti-apoptotic Bcl-2/Bax ratio and decreased p21 and caspase-3 expression in senescent mice (211). The study's utilization of senescent mice suggests a potential relevance of senescence to COPD pathology, although further investigation is necessary to substantiate this hypothesis.

Endoplasmic Reticulum Stress-Induced Apoptosis

Chronic oxidative stress and inflammation in COPD triggers endoplasmatic reticulum (ER) stress and activates the unfolded protein response, which shifts toward apoptosis under persistent stress. Key mediators include transcription factor C/EBP Homologous Protein (CHOP) and caspase-12, all of which contribute to epithelial and endothelial cell death (212). SIRT1 has been shown to attenuate ER stress-induced apoptosis by suppressing CHOP expression through FOXO-dependent mechanisms, thereby limiting pro-apoptotic signals (213).

Wang et al. (2020) demonstrated that CSE suppresses SIRT1 in lung cells, which triggers ER stress and apoptosis. In vivo, a COPD rat model was established by combining lipopolysaccharide instillation with 28 days of CS exposure. In vitro, human alveolar epithelial cells were exposed to CSE to induce a COPD-like state. The study showed that SIRT1 deficiency upregulates ER stress markers, such as CHOP, and activates the ER stress-mediated apoptotic pathway, increasing caspase-12 and caspase-3 (214).

Zhang et al. (2020) proved that activating SIRT1 significantly reduced ER stress and apoptosis in the lung tissues of rats with COPD. This reduction directly correlated with

improved lung function, suggesting that SIRT1 plays a protective role against cellular damage associated with COPD (215).

4.1.6. Epigenetic and Metabolic Reprogramming Pathways

Histone Modification

COPD patients manifest an epigenetic shift that favors histone acetylation, resulting in dysregulation of inflammatory genes. Histone acetylation, particularly on histones H3 and H4, serves as a critical regulatory mechanism (216).
SIRT1 deacetylates histones H3 and H4 at inflammatory gene promoters, thereby suppressing NF-κB signaling and limiting proinflammatory gene expression (217).

Noh et al. (2024) investigated the epigenetic mechanisms underlying PM-induced COPD. Mice were exposed to PM for a period of 4 to 8 weeks, while murine alveolar macrophages were treated with PM for 4 weeks in vitro. The study confirmed reduced SIRT1 expression in pulmonary macrophages from COPD patients compared to the control group. The research indicated that chronic PM exposure resulted in histone H4 hyperacetylation, specifically at lysine 8 (H4K8ac), in macrophages, which in turn drove the expression of pro-inflammatory genes. This hyperacetylation was caused by reduced SIRT1 activity, which was, in turn, caused by PM-induced depletion of NAD+. The results of the study demonstrated that SIRT1 expression or treatment with resveratrol, a known activator of SIRT1, led to the reversal of H4K8ac and inflammation (218).

NAD^+-SIRT1-PGC-1α Axis

The NAD^+-SIRT1-PGC-1α axis in COPD affects both mitochondrial dysfunction and energy imbalance. Levels of PGC-1α have shown to gradually decrease as COPD progresses (219). SIRT1 activates PGC-1α via deacetylation, enhancing mitochondrial respiration and fatty acid oxidation. Under conditions of oxidative stress, reduced SIRT1 levels impair PGC-1α function, leading to bioenergetic failure and ROS accumulation (220).

Mao et al. (2020) found that upregulating SIRT1 expression in muscle cells is associated with elevated PGC-1α levels. Rats skeletal muscle cells were utilized and exposed to CSE to induce a condition of muscle injury that is analogous to that observed in patients with COPD. The rats were then treated with a serum containing Bufei Jianpi Formula, a traditional Chinese herbal medicine. The study's primary outcomes included enhanced lung

and muscle function, restored mitochondrial respiration, and mitigated muscle atrophy. It demonstrates that the SIRT1–PGC-1α axis, which is known to play a protective role, is impaired in the context of COPD-related muscle wasting (221).

	Roles in COPD	Modulation of Key Pathways
SIRT1	Inflammation	Suppressing NF-κB activity and reducing the release of inflammatory cytokines Inhibiting NLRP3 inflammasome activity Suppressing MAPK-mediated airway inflammation Disrupting NF-κB regulation through PI3K/AKT/mTOR signaling Suppressing inflammatory response by inhibiting histone hyperacetylation
	Oxidative stress	Neutralizing ROS through enhancing Nrf2/HO-1 signaling Reducing ROS levels by modulating PGC-1α activity
	Mitochondrial metabolism	Restoring mitochondrial respiration through PGC-1α
	Apoptosis	Suppressing apoptosis through p53 and FOXO3 Inhibiting miR-132-driven apoptosis and FOXO1 Inhibiting ER stress-induced apoptosis by suppressing CHOP
	Senescence	Inhibiting cell cycle arrest Regulating DNA repair through DDR/p53 signaling Suppressing SASP response Regulating senescence through miR-570-3p Inhibiting miR-125a-5p-driven senescence
SIRT2	Inflammation	Suppressing NF-κB activity
SIRT3	Oxidative stress	Activating MnSOD and reducing oxidative damage Regulating mitochondrial dysfunction through PI3K/AKT/mTOR signaling
	Mitochondrial metabolism	Activating SOD2 to neutralize superoxide radicals
	Apoptosis	Suppressing cell death via caspase 3-pathway
	Epithelial injury	Inhibiting ferroptosis through Nrf-2/SIRT3-iNOS pathway
	Senescence	Suppressing senescence markers through miR-494-3p
SIRT4	Oxidative stress	Inhibiting ferroptosis activated through ROS
	Energy metabolism	Regulating mitochondrial dysfunction and energy production
SIRT6	Senescence	Inhibiting senescence with PI3K pathway genes Suppressing SASP response

Table 3 *Sirtuin-Mediated Regulation of Pathological Mechanisms in COPD according to research from 2019-2025 (data sourced from Li et al. (2023) (147))*

4.2. Crosstalk

The functional complexity of sirtuins extends beyond the scope of their individual roles. Research has demonstrated the presence of shared mechanisms and coordinated crosstalk among these cells, facilitating their regulation of pivotal pathophysiological processes in COPD through interconnected pathways.

As demonstrated in this work, multiple sirtuins exert their influence on oxidative stress, inflammation, mitochondrial dysfunction, and cellular senescence by acting within the same signaling cascades. SIRT1, SIRT3, and SIRT6 have been implicated in the regulation of ROS detoxification and DNA repair. SIRT1 has been shown to enhance oxidative stress resistance by activating FOXO3 and Nrf2. SIRT3 has been demonstrated to act directly on mitochondrial antioxidant enzymes, including SOD2. These functions converge. Additionally, Meng et al. (2020) discovered the cooperation between SIRT1 and SIRT6 in the regulation of DNA double strand breaks. They showed that SIRT1 deacetylates SIRT6 at lysine 33, initiating together the DNA damage response and chromatin remodeling (222). Additionally, both SIRT1 and SIRT2 have been shown to interact with NF-κB signaling, thereby offering a complementary suppression of inflammatory gene expression. The observation of shared functions among sirtuins indicates their operation as a coordinated network rather than in isolation (223).

Beyond these shared mechanisms, there is evidence that the loss of one sirtuin can lead to the upregulation of another as part of a compensatory response (224).

In contrast, SIRT2 and SIRT3 appear to operate in separate compartments, exhibiting functional antagonism during inflammatory polarization. SIRT2 inhibition has been demonstrated to reduce M1 macrophage activation (225), while SIRT3 expression has been shown to suppress inflammatory responses (226).

Studies have shown that global NAD^+ depletion or CD38 overactivation simultaneously impairs multiple sirtuins, supporting the idea that their functions are coordinately regulated by metabolic status (227).

Furthermore, there is growing evidence that SIRT5 modulates SIRT3 activity through competitive lysine modifications. This suggests that non-acetylation-based PTMs add another layer of complexity to mitochondrial regulation (228).

This interplay opens new avenues for multi-pathway targeting strategies, wherein interventions that enhance global sirtuin function could provide broader therapeutic benefits than modulating a single isoform.

4.3. Dual Roles

Sirtuins not only as protective regulators of cellular homeostasis but also as contributors to tissue damage under certain conditions. This duality is indicative of the intricate interplay between redox status, inflammation, and metabolic adaptation in the diseased lung. In this context, sirtuins have been observed to exert divergent effects, contingent on isoform, subcellular localization, and disease progression stage.

It is known that SIRT3 has been shown to exhibit antioxidant and anti-apoptotic effects through its regulation of SOD2 and cyclophilin D (188).

However, paradoxical observations have been documented. Guan et al. (2021) show that elevated levels of SIRT3 lead to inflammasome activation in macrophages (229).

SIRT2 also exhibits functional duality, supporting microtubule stability and mitotic regulation in the early stages of the disease process, yet promoting pro-inflammatory responses during staphylococcal infection (230).

Chen et al. (2023) discovered that SIRT6 promotes PM2.5-induced airway inflammation in macrophages through its epigenetic regulatory function. In contrast to its conventional anti-inflammatory function, SIRT6 deletion in myeloid cells led to a decrease in inflammatory cytokine production. These findings suggest that the inhibition of its epigenetic activity may have therapeutic potential in pollution-driven airway diseases, such as COPD (231).

The recognition of these dual roles supports the shift toward isoform-specific and context-dependent therapies of future precision medicine approaches in COPD.

4.4. Driver or just a Bystander?

The role of sirtuins in the pathogenesis of COPD remains a subject of active investigation, with ongoing discourse surrounding their potential as active drivers to disease development or as a consequence of secondary changes. Recent findings indicate that multiple sirtuins, notably SIRT1 and SIRT3, do not serve as passive indicators.

As described previously, a body of research has demonstrated a correlation between diminished SIRT1 and SIRT3 expression and activity and impaired antioxidant defenses, enhanced NF-κB signaling, and accelerated epithelial cell senescence. These phenomena are pivotal to the progression of COPD.

Also, genetic and epigenetic variations affecting sirtuin expression suggest that altered sirtuin function may predispose individuals to COPD or influence disease severity (208).

Conversely, certain studies posit that sirtuin dysregulation may not be a primary factor in the development of the condition. Rather, sirtuin dysregulation could be a secondary consequence of chronic oxidative stress and NAD^+ depletion. This viewpoint is substantiated by research findings indicating a decline in sirtuin levels in the advanced stages of COPD (232). This decline is presumably attributable to protracted exposure to cigarette smoke and systemic inflammation.

Therefore, while some sirtuins appear to actively modulate COPD-relevant pathways, others may become downstream victims of disease progression. This finding indicates a context-dependent dual nature.

5. Therapeutic Synopsis Targeting Sirtuins

This section provides an overview of knowledge on the therapeutic targeting of sirtuins. Topics include druggability, existing and emerging therapeutic strategies, and the feasibility of developing sirtuin-based treatments for COPD.
Subsequent subsections will explore the pharmacological modulation of sirtuins, therapeutic approaches, available compounds, and novel agents under investigation.

5.1. Can SIRTs be Pharmacologically Targeted?

A growing body of evidence from preclinical models and in vitro systems has identified several chemical agents that interact with sirtuin proteins, suggesting their therapeutic potential. Consequently, this research has spurred the development and evaluation of various pharmacological agents in diverse disease contexts, including metabolic disorders, neurodegenerative diseases, and, most recently, chronic inflammatory conditions, such as COPD.
Despite challenges in terms of specificity and clinical translation, data suggest that sirtuins are biologically relevant to disease pathogenesis and amenable to targeted, drug-based interventions (147).

5.2. Therapy Approaches

A variety of therapeutic strategies have been developed to modulate sirtuin activity. These strategies differ in their mechanisms of action and molecular targets and can be broadly categorized into three main types: activators, inhibitors, and indirect modulators.
Activators enhance the function of sirtuins by increasing their enzymatic activity. This enhancement is often achieved through direct interaction with the protein or by influencing its cofactor environment (233).
In contrast, inhibitors are designed to suppress sirtuin activity, either selectively or broadly, by interfering with catalytic function or substrate binding (233).
The third category comprises indirect modulators, which influence sirtuin activity by altering cellular conditions, such as NAD^+ availability, rather than acting directly on sirtuins (234).
These diverse approaches enable flexible targeting of sirtuins, depending on the desired biological outcome and disease context. Understanding these mechanistic differences is

crucial for selecting suitable therapeutic strategies and interpreting their potential implications in experimental and clinical contexts.

5.3. Existing Therapeutics

Although there is no sirtuin-targeting therapy that has been approved to treat COPD, several compounds that affect sirtuin pathways are used in clinical settings for other purposes and have been studied in relation to respiratory diseases, including COPD.

Resveratrol, a natural SIRT1 activator and one of the naturally existing polyphenols in plants, is one such compound. It has been the subject of small clinical studies and is available as a dietary supplement. Zeng et al. (2022) found in a preclinical study that resveratrol reduces cigarette smoke-induced cellular aging in human airway cells by targeting the miRNA-34a/SIRT1/NF-κB pathway. Resveratrol reversed the effects of smoking by lowering senescence markers, reducing inflammatory cytokines, and increasing SIRT1 (201). Prior to this, another study by Wang et al. (2017) already demonstrated that resveratrol improves COPD pathogenesis in a rat model by activating the SIRT1/PGC-1α signaling pathway, which mitigates oxidative stress and inflammation. The researchers found that resveratrol treatment increased SIRT1 and PGC-1α expression in lung tissue, which correlated with reduced oxidative damage and decreased pro-inflammatory cytokines (IL-6 and IL-8) in the serum (235).

Other natural polyphenolic compounds, such as curcumin, was shown to mitigate COPD by activating the SIRT1 pathway (236). These findings have prompted the initiation of early-phase trials to evaluate Resveratrol's potential impact on systemic inflammation and oxidative stress in chronic lung diseases (237).

Metformin, a widely prescribed antidiabetic drug that modulates cellular energy metabolism, has been associated with improved outcomes in patients with COPD and comorbid diabetes. It has been demonstrated to impede endothelial senescence induced by high glucose-mediated metabolic memory. This effect is achieved through the modulation of the SIRT1/p300/p53/p21 pathway (238). Polverino et al. (2021) demonstrated that metformin protects against CS-induced emphysema in mice by increasing SIRT1 levels and activating AMPK, thereby reducing inflammation, ER stress, oxidative damage, and cellular aging (239). Notably, this mechanism was observed to translate to humans, where the use of

metformin in the COPD Gene cohort was associated with a significantly slower progression of emphysema (240).

Preliminary research has indicated that melatonin may play a role in the prevention of the development of COPD. He et al. (2019) demonstrated that melatonin ameliorates COPD in rats through suppression of endoplasmic reticulum stress and apoptosis of lung cells, a process that is mediated through upregulation of SIRT1 (241).

5.4. Emerging Therapies

5.4.1. Novel Small-Molecule Activators

The most studied compounds of small-molecule activators are synthetic analogs of resveratrol, such as SRT2104 and SRT1720, which have shown promise in enhancing SIRT1 function in experimental models of lung injury induced by cigarette smoke (242).

Wang et al. (2021) showed that treating mice exposed to long-term cigarette smoke with SRT2104 significantly reduced NF-κB signaling, improved mitochondrial biogenesis, and decreased alveolar cell death. In addition, Yuan et al. (2021) demonstrated that type II alveolar epithelial cells (ATII) induced by cigarette smoke exhibited increased senescence. Conversely, SIRT1 activation with SRT2104 significantly reduced the levels of senescence in the cells (243). Also, Gu et al. (2020) reported that the SIRT1 activator SRT2104 mitigates emphysema pathology and enhances lung function in rats by suppressing senescence of alveolar epithelial cells. This protective effect was mediated through SRT2104-induced upregulation of SIRT1 activity, highlighting its therapeutic potential for COPD (244).

Similarly, Zhang et al. (2021) demonstrated in vitro that the SRT1720 countered CSE-induced senescence in alveolar epithelial cells by restoring autophagy. The reactivation of SIRT1 activity by SRT1720 resulted in the restoration of key autophagy genes. It is imperative to note that the restoration of autophagy was found to be essential in the reduction of senescence markers (245).

Recently, efforts have focused on isoform-selective activators, with emerging interest in SIRT3-targeting molecules like honokiol, isolated from Magnolia species, which enhances mitochondrial antioxidant defenses and reduces ROS accumulation in airway epithelial cells (246). Li et al. (2023) demonstrated that honokiol protects airway epithelial cells from CSE-

induced mitochondrial damage. This protection is achieved through the specific upregulation of SIRT3 expression and the SIRT3/SOD2 pathway (247).

Xu et al. (2023) identified selective SIRT6 activators that exhibited potent inhibitory effects on the production of pro-inflammatory cytokines in vitro. Further investigation in animal models is necessary to determine the full potential of these activators (248).

To date, the investigation of other mitochondrial SIRT3 and SIRT5 activators, such as Compound 31 and 30, has been conducted in the context of breast cancer cells (249).
While most sirtuin activators remain in preclinical testing, some, including resveratrol and its derivatives, have entered Phase III trials for metabolic diseases (250).

5.4.2. NAD^+ Boosters

Because all sirtuins depend on NAD^+, strategies that increase intracellular NAD^+ levels are a promising way to support sirtuin function overall. Key candidates include nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN).

Slama et al. (2024) investigated the preventive effect of NADH supplementation in mice exposed to CSE. The results of the study showed that NADH significantly preserved lung antioxidant defenses while reducing oxidative damage markers and attenuating inflammation (251).

Notably, NMN has been observed to restore declining NAD^+ levels in aging models, thereby enhancing the activity of sirtuin deacetylases, particularly SIRT1 (252).
Zhang et al. (2021) demonstrated that both the NAD^+ precursor NMN and the PARP1 inhibitor Olaparib restore SIRT1 activity in cells exposed to CSE by rescuing the NAD^+/NADH ratio. The restoration of SIRT1 activity has been demonstrated to induce autophagy and to impede SIRT1-dependent cellular senescence (245).

Norheim et al. (2024) conducted a randomized, double-blind, placebo-controlled trial to investigate the effects of NR. Forty stable COPD patients received either NR or placebo for a period of six weeks, with a 12-week follow-up period. The study demonstrated that NR significantly reduced sputum IL-8. However, no enhancements in lung function or symptoms were detected. While this finding suggests the potential for targeting airway inflammation in COPD, the necessity for larger trials is paramount to substantiate the clinical relevance (253).

5.4.3. Sirtuin Inhibitors

In contrast to activators, sirtuin inhibitors are being studied in contexts where excessive sirtuin activity contributes to disease progression, such as fibrosis, apoptosis, and immune dysregulation. Studies have demonstrated that SIRT2 expression is elevated in fibrogenic human lung fibroblasts (254).

Of the inhibitors under consideration, EX527, a selective SIRT1 inhibitor, and AGK2, a selective SIRT2 inhibitor, have received the most extensive research attention. EX527 has been evaluated in cancer and fibrotic models, indicating its capacity to regulate p53 (255).
In the context of lung-specific research, AGK2 has garnered interest due to its capacity to impede the release of pro-inflammatory cytokines, particularly in models of airway inflammation. The results of the study demonstrate that the effect of AGK2 is achieved through the suppression of NF-κB and the elevation of NRF2 (256).

The study by Yadav et al. (2024) demonstrates that inhibiting SIRT-2 with the specific inhibitor AK-7 significantly reduces airway inflammation and oxidative stress in a murine model of COPD. This reduction may be due to modulation of the NF-κB and MAPK signaling pathways. AK-7 administration was found to decrease pro-inflammatory cytokines, immune cell infiltration, and lung tissue damage while enhancing anti-inflammatory and antioxidant responses (257).

5.4.4. Mitochondrial Peptides

Mitochondrial dysfunction as a central mechanism in the pathogenesis of COPD makes SIRT3-targeted therapies relevant. Compounds such as SS-31, also known as elamipretide, function as mitochondria-targeted antioxidants, emulating the effects of SIRT3.

A study by Yang et al. (2021) demonstrated that SS-31 attenuates CS-induced airway inflammation and oxidative stress in both mice and bronchial epithelial cells. SS-31 has been demonstrated to reduce inflammatory cell infiltration, proinflammatory cytokines, and oxidative markers, while concomitantly restoring antioxidant SOD activity (258).

Additionally, researchers have explored small-molecule enhancers of SIRT3, such as MitoTEMPO conjugated compounds, which combine mitochondrial targeting with antioxidant activity to reduce ROS levels induced by CSE in vitro (259).

5.4.5. Gene-Based Strategies

Recent advances in molecular biology have enabled novel approaches to modulate sirtuin expression at the genetic and epigenetic levels.

One such strategy is CRISPR/dCas9-mediated gene activation, which may enhance endogenous sirtuin promoters without editing (260).

Another promising approach uses adeno-associated virus (AAV)-based delivery systems, which employ vectors such as AAV9 and AAV2/8 to restore depleted sirtuin levels, particularly SIRT1 and SIRT3, which are downregulated in COPD lungs. Experimental models have shown that AAV2- SIRT1 treatment increased retinal SIRT1 expression in mice (261). Further investigation is necessary to better understand the complex mechanisms underlying COPD models.

Conversely, gene delivery through lentiviral vectors has the potential to influence the future of sirtuin-targeted therapy. Research has demonstrated the efficacy of α1 antitrypsin lentiviral vectors as well as AAV2/8 in ameliorating emphysema in murine models (262,263).

The potential of lentiviral transduction of sirtuins remains to be elucidated in suitable experimental models.

5.4.6. Nanoparticle and Targeted Delivery System

To enhance therapeutic efficacy and minimize systemic side effects, it is necessary to develop tissue-specific delivery systems for pulmonary administration. These systems include liposomal carriers, nanoparticle formulations, and targeted aerosol delivery of sirtuin-modulating agents.

The utilization of liposomes in gene therapy for COPD entails the employment of their intrinsic lipid bilayer configuration which facilitates the efficient delivery of genetic material into target cells. Kawakami et al. (2025) revealed that liposomes containing NMN exhibited higher levels of NAD^+ than non-liposomal NMN (264).

Another approach involves polymeric nanoparticles. Nanoparticles leverage their nanoscale size for efficient, targeted gene delivery to epithelial cells in COPD. Engineered with coatings, they overcome the disease's thickened mucus barrier while offering biocompatibility and biodegradability (265). The development and testing of nanoparticles

loaded with SIRT1 is underway in the context of various diseases, including atherosclerosis (266).

These delivery systems aim to address the challenges of systemic toxicity, poor bioavailability, and non-specific targeting associated with conventional methods.

6. Discussion

To summarize, COPD is driven by a complex interplay of immune activation, oxidative stress, mitochondrial dysfunction, and cellular senescence. All these processes contribute to progressive lung damage and inflammation. Within this framework, sirtuins have emerged as key molecular regulators influencing several disease mechanisms across multiple compartments.

Notably, SIRT1, SIRT3, and SIRT6 have been identified as central players. SIRT1 modulates NF-κB signaling and DNA repair, SIRT3 regulates mitochondrial redox balance and apoptosis, and SIRT6 influences chromatin remodeling and aging-related decline. Their involvement suggests that sirtuins are not passive markers but actively participate in shaping the molecular landscape of COPD, offering mechanistic insight into how these pathways intersect and drive disease progression. This understanding sets the stage for exploring their therapeutic potential in later sections. In addition to their anti-inflammatory and antioxidant roles, certain sirtuins exhibit dual functions depending on environmental stressors. SIRT2 and SIRT6 have demonstrated context-dependent roles, where their inhibition or activation can either reduce or exacerbate inflammation, underscoring the need for isoform-specific and stage-dependent therapeutic strategies.

In recent years our understanding of sirtuin biology in pulmonary pathology has significantly advanced. One major strength lies in the identification of SIRT1 and SIRT3 as mediators of mitochondrial function and antioxidant defense. Additionally, the recognition of SIRT6 as a regulator of DNA repair and chromatin stability adds another layer of relevance, especially in the context of accelerated lung aging. Importantly, research has demonstrated crosstalk between sirtuins and central signaling pathways, such as NF-κB, Nrf2/HO-1, and PGC-1α, positioning them as integrators of metabolic and inflammatory responses. There is less research ongoing for SIRT7 in COPD. A recent work Wyman et al. (2020) about pulmonary fibrosis with pulmonary endothelial cells implicate that SIRT7 downregulation mimicked cellular aging. SIRT7 loss triggered the process of endothelial-to-mesenchymal- cell transition, making the cells more fibrous. This finding indicates a potential correlation between a decline in SIRT7 and the development of pulmonary fibrosis and acute lung injury, which may also contribute to the pathogenesis of COPD (267).

All these findings have opened new avenues for targeted therapeutic development, particularly in pathways that are both well-characterized and druggable. Among these, the SIRT1-NF-κB axis, the SIRT3-SOD2 mitochondrial antioxidant pathway, and the NAD^+-dependent regulation of metabolic homeostasis stand out as the most promising targets due to their involvement in inflammation, oxidative stress, and cell survival. Modulation of NF-κB signaling via SIRT1 remains one of the best-supported approaches, with experimental models showing that SIRT1 activators like SRT2104 or resveratrol analogs can suppress chronic inflammation and improve lung function in smoke-exposed animals. These findings underscore the significance of sirtuin-mediated inhibition of NF-κB in maintaining immune homeostasis and averting excessive inflammation (268). The bioavailability and pharmacodynamics of resveratrol itself are suboptimal, as it is characterized by poor oral bioavailability and limited pharmacodynamic potency (269). While preclinical studies of resveratrol and its analogues still suggest significant benefits (270), clinical evidence in COPD patients presents a more complex picture. A double-blind randomized controlled trial (RCT) by Beijers et al. (2020) found that four weeks of resveratrol supplementation (150 mg/day) did not improve muscle mitochondrial function, including SIRT1/PGC-1α pathways, or inflammation in COPD patients. Notably, resveratrol supplementation induced significant lean mass loss compared to the placebo group, raising a critical concern for this population (271). Other advancements in polyphenols derived from Chinese herbal medicine (CHM). It reveals promising prospects for the management of COPD with polyphenolic compounds by reducing airway inflammation, oxidative stress, and cell death (236).
Xiong et al. (2021) and Tao et al. (2023) demonstrated that CHM treatment not only improved clinical symptoms and quality of life, but also reduced the frequency of acute exacerbations in patients with COPD, as well as the risk of mortality (237,272).

Beyond single-pathway targeting, the concept of multi-pathway targeting reflects a shift toward network-level modulation and precision medicine. Dual activation of SIRT1 and SIRT3 may synergistically reduce inflammation and modulate mitochondrial biogenesis (273).

On the other hand, the concept of integrating targeted therapy with sirtuins with existing therapeutic modalities, specifically steroid therapy, is a subject of ongoing research investigation. A notable challenge in this approach involves the management of steroid resistance in pro-inflammatory lymphocytes. In order to address this knowledge gap, Hodge et al. (2020) established a correlation between SIRT1 deficiency in pro-inflammatory

CD28nullCD8+ T- and natural killer T-like lymphocytes and steroid resistance in COPD. They showed that SIRT1 activators, including resveratrol and curcumin, in combination with prednisolone successfully restored steroid sensitivity and reduced cytokines via SIRT1-dependent mechanisms. This finding provides a novel strategy to overcome steroid resistance (274).

Research on sirtuins in other chronic conditions must be taken into account. Studies in metabolic diseases, neurodegeneration, and cancer have provided valuable insights into the mechanistic versatility of sirtuins and their therapeutic potential beyond respiratory pathology. SIRT1 and SIRT6 have been extensively studied in type 2 diabetes and obesity (275). In neurodegenerative diseases such as Alzheimer's and Parkinson's, SIRT2 inhibition has emerged as a promising strategy to reduce neuroinflammation and improve proteotoxic stress responses (276). Similarly, SIRT3 activators and mitochondria-targeted antioxidants are being explored in cardiovascular disease and cancer, offering potential translational relevance for reducing oxidative stress in emphysematous lungs (277). The mechanistic overlap between COPD and these conditions is particularly evident in pathways involving oxidative stress response, NF-κB signaling, mitochondrial health, and cellular senescence, all of which are modulated by sirtuins across disease models. This suggests that therapeutic strategies targeting these mechanisms could be repurposed or adapted for pulmonary applications.

Though, some limitations must be acknowledged when interpreting the current research that can be found. First, the majority of the reviewed studies are preclinical, relying on cell culture models or rodent systems that may not fully reflect the heterogeneity of human COPD phenotypes. Second, much of the literature centers on SIRT1 and SIRT3, while other isoforms such as SIRT4, SIRT5, and SIRT7 remain understudied in pulmonary contexts, limiting our understanding of their potential roles in metabolic metabolism, nucleolar stress, and age-related decline in COPD. Furthermore, many studies report sirtuin expression levels or activity changes, but few establish causal relationships or explore temporal dynamics, such as whether altered sirtuin function precedes or follows key pathological events. Another critical methodological consideration is the lack of standardized tools for measuring sirtuin activity in clinical samples. Most research relies on mRNA expression or protein abundance, which do not always correlate with enzymatic activity. This limitation affects the reliability of using sirtuins as biomarkers or therapeutic targets without direct functional assessment.

Additionally, the field faces challenges in isoform-specific targeting. The development of more selective compounds, particularly those enabling tissue- and cell-specific delivery, remains an important unmet need for future research.

Finally, while efforts were made to include gene-level evidence, epigenetic regulation, and pathway crosstalk, some findings may represent context-specific observations rather than universal mechanisms. Therefore, further human-based investigations are essential to validate these pathways and assess their utility in guiding precision therapies in COPD.

7. Outlook and Final Synthesis

The future of targeted therapy in COPD is increasingly shifting toward precision medicine, aiming to tailor interventions based on individual patient profiles, including genetic, epigenetic, and molecular characteristics. Advances in the field of biomarker discovery are expected to play a central role in identifying subpopulations of patients who may benefit most from specific therapies, including those targeting sirtuins or other regulatory pathways (278).

Another important trend is the integration of multi-omics technologies. Multi-omics technologies are a set of techniques that integrate genomics, transcriptomics, proteomics, and metabolomics. These technologies facilitate the identification of distinct types of COPD and the development of targeted, personalized therapies (279). Furthermore, nanotechnology-based drug delivery systems are being developed to enhance the specificity and efficacy of therapeutics by directing them to affected lung tissues while minimizing systemic exposure. Innovations such as CRISPR/Cas9-mediated gene editing, mRNA-based therapeutics, and artificial intelligence-driven drug discovery are also gaining traction in respiratory research, offering potential breakthroughs in modulating previously undruggable targets (280). In addition, combination therapies that address multiple pathological mechanisms are being explored to overcome the complex heterogeneity of COPD (281). Collectively, these emerging strategies hold promises for developing more effective, personalized, and mechanism-based treatments that go beyond mere symptom management toward disease modification.

This thesis has provided a comprehensive overview of COPD, from its clinical and pathophysiological foundations to the emerging role of sirtuins in disease mechanisms and therapeutic targeting. By synthesizing current knowledge on key pathological processes this work highlights how these interconnected pathways contribute to disease progression and heterogeneity. The exploration of both existing and emerging therapeutic strategies further underscores the growing feasibility of pharmacologically modulating sirtuin activity, offering novel opportunities for intervention in COPD. However, significant challenges persist. The state of research is encumbered by inconsistencies in experimental models, lacunae in clinical translation, and an incomplete understanding of sirtuin crosstalk within complex signaling networks. Consequently, future interdisciplinary endeavors must

prioritize the identification of methodologies that facilitate the integration of multi-omics data, fostering collaborative research initiatives.

Advancing our understanding of sirtuins in COPD is of paramount importance. By deepening our mechanistic insight, we can move closer to the vision of precision-based respiratory medicine.

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