

Targeting Non-Eosinophilic Immunological Pathways in COPD and AECOPD: Current Insights and Therapeutic Strategies

Dur E Maknoon Razia¹, Chencheng Gao¹, Chao Wang¹, Yiming An¹, Fang Wang¹⁻³, Ling Liu¹, Hongqiang Lin¹⁻³

¹College of Basic Medical Sciences, Jilin University, Changchun, 130021, People's Republic of China; ²Jilin Provincial Science and Technology Innovation Centre for Secondary Development of Proprietary Chinese Medicines, Changchun, 130021, People's Republic of China; ³Jilin Provincial Engineering Laboratory of Precision Prevention and Control for Common Diseases, Changchun, 130021, People's Republic of China

Correspondence: Ling Liu; Hongqiang Lin, College of Basic Medical Sciences, Jilin University, Xinmin Road 126, Changchun, 130021, People's Republic of China, Tel +86 431 85619574, Email liuling1978@163.com; linhq@jlu.edu.cn

Abstract: COPD is a multifactorial illness characterized by a long-term restriction of airflow and an inflammatory reaction in the lungs. The associated emphysema leads to the breakdown of alveolar proteins and abnormal expansion of the lung air spaces. Chronic bronchitis caused by the same disease can result in increased deposition of structural proteins, narrowing of the airways, and excessive mucus secretion leading to acute exacerbation of COPD (AECOPD). The most commonly prescribed medications for it, such as glucocorticoids and bronchodilators, provide important therapeutic benefits, but they also have negative side effects, including immunosuppression and infection. Therefore, it is necessary to develop medications for the treatment of COPD that specifically target the immune system and molecular components. This review focuses on non-eosinophilic aspects of immunological modulation in COPD management. Since, existing literature extensively covers eosinophilic inflammation, this review aims to fill the gap by examining alternative immunological pathways and their therapeutic implications. The findings suggest that targeting specific immune responses may enhance treatment efficacy while minimizing adverse effects associated with traditional therapies. In summary, this review emphasizes the importance of advancing research into non-eosinophilic immunological mechanisms in COPD, prescribing for the development of novel therapies that can more effectively manage this disease.

Keywords: COPD, AECOPD, immunological targets, emerging therapeutic strategies

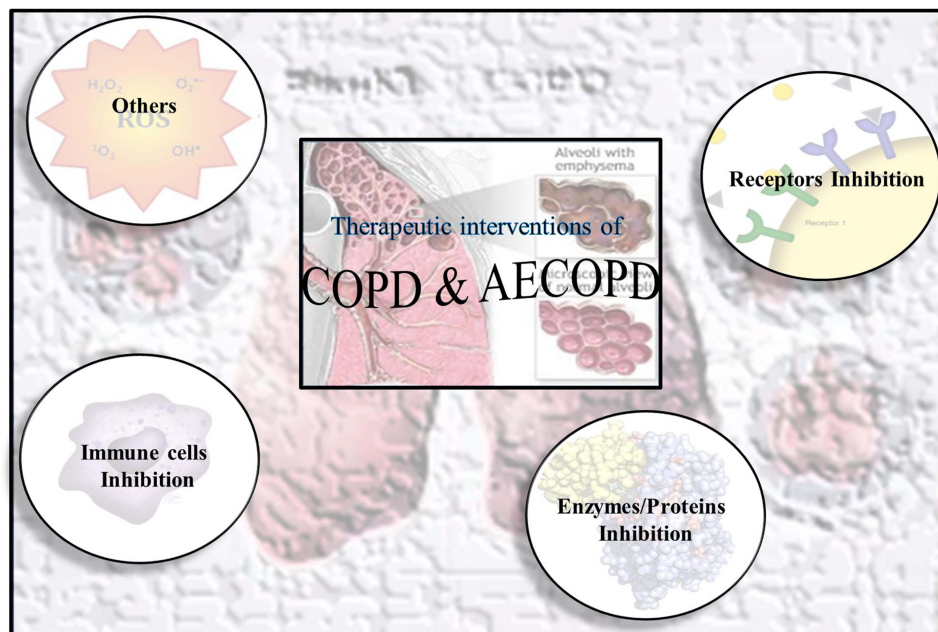
Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive, long-term respiratory disorder characterized by persistent breathing difficulties and restricted airflow, which worsen over time.¹ The primary cause of COPD is predominantly linked to cigarette smoking, making it a major public health concern. In 2010, COPD ranked as the fourth leading cause of death worldwide, and projections indicated it has become the third leading cause by 2020.² These exacerbations are not only costly but are also linked to increased mortality, underscoring the need for effective management strategies. Chronic obstructive pulmonary disease affects approximately 350 million people globally, although prevalence estimates vary widely across different regions and countries.³

The disease manifests in various forms, primarily emphysema and chronic bronchitis, leading to symptoms such as chronic cough, excessive mucus production, and difficulty breathing.⁴ One of the most severe manifestations of this disease is an acute exacerbation of chronic obstructive pulmonary disease (AECOPD), a temporary worsening of symptoms that can sometimes require hospitalization. These exacerbations are costly and linked to increased mortality, underscoring the need for effective management strategies.⁵

Existing treatments for COPD are largely aimed at managing symptoms, as well as preventing exacerbations. The core components of COPD therapy include combinations of bronchodilators, such as long-acting β 2-agonists (LABA)

Graphical Abstract



and long-acting anti-muscarinic agonists (LAMA), alongside corticosteroids (inhaled or oral) antibiotics⁶ mucolytics, and macrolides for patients with frequent exacerbations.⁷ However, these treatments carry significant risks. Corticosteroid use, for instance, increases the likelihood of pneumonia and mycobacterial infections by approximately 2 to 4 times in COPD patients.⁸ Additionally, broad-spectrum antibiotics do not reduce hospitalization duration, 30- or 90-day readmission rates, time to the next exacerbation, or mortality in non-ICU COPD patients. Moreover, these antibiotics are associated with adverse effects, such as diarrhea, skin rashes, and the development of antibiotic resistance among respiratory pathogens.^{6,9}

This demonstrates the complexity of COPD, highlighting that a uniform approach to treatment often results in diverse outcomes, such as treatment intolerance, non-response, and unequal access to therapies.¹⁰ Therefore, there is an urgent need for innovative therapeutic approaches that target the underlying mechanisms of COPD rather than solely addressing symptoms.

Recent developments have focused on alternative strategies less prone to fostering antimicrobial resistance. These approaches aim to inhibit disease progression by targeting mechanisms that pathogens find harder to adapt to.¹¹ Novel therapies are emerging that disrupt crucial microbial processes, such as inhibiting attachment and invasion or enhancing pathogen clearance by the immune system, representing a significant shift from traditional treatments.¹²

In summary, given the heterogeneous nature of COPD, it is essential to move beyond conventional symptom-focused treatments. This review summarizes the risk factors associated with COPD, outlines therapeutic strategies for managing non-eosinophilic COPD and AECOPD, and explores emerging approaches that focus on immunological mechanisms. These novel strategies include the inhibition of key receptors (PAFr, ICAM-1, SA, and TLR), the targeting of critical proteins and enzymes (PKC, PKI3, EGFR, ST6GAL1, and annexin-1), the modulation of immune cells (such as macrophages), and the control of other factors, including oxidative stress and iron levels. Through these advances, there is hope for more effective and individualized treatments for COPD in the future.

Etiologies of COPD

Smoking remains the primary cause of COPD, with its effects often manifesting later in life.¹³ In recent years, significant progress has been made in understanding the causes and risk factors associated with COPD, especially through

epidemiological research. However, ongoing research is essential to further refine treatment and management strategies for both individuals and the broader population. The increasing prevalence of COPD places a substantial burden on healthcare resources and has significant economic implications worldwide. Multiple risk factors, including comorbidities and environmental exposures, contribute to the exacerbations of COPD. These exacerbations, along with conventional therapies for managing COPD and AECOPD, are outlined in [Table 1](#) and [Table 2](#), respectively.

Immunological Targets

Receptors

Platelet-Activating Factor Receptor (PAFr)

Platelet-activating factor (PAF) is a phospholipid mediator critical in inflammatory processes, acting on various cells such as platelets, endothelial cells, lymphocytes, and macrophages.^{45,46} Elevated PAF receptor (PAFr) expression in COPD patients' respiratory tracts facilitates bacterial adherence and proliferation, contributing to acute and chronic respiratory infections.⁴⁷ Pathogens like *Streptococcus pneumoniae* and *Haemophilus influenzae* interact with PAFr,⁴⁸ activating intracellular pathways (eg, Ras/Raf, PI3K, Rho/Rec1), leading to cytoskeletal remodeling, enhanced pathogen survival, and membrane ruffling ([Figure 1](#)).

Environmental factors, including cigarette smoke, air pollution, and e-cigarette vapor, significantly elevate PAFr expression.^{49,50} Laboratory studies suggest nicotine may play a role in PAFr upregulation observed in nasal epithelial cells exposed to e-cigarette vapor. Similarly, cigarette smoke extract (CSE) has been shown to enhance the adhesion of *S. pneumoniae* and *H. influenzae* to human bronchial epithelial cells via PAFr.⁵¹

Studies also indicate that PAFr expression may contribute to other respiratory conditions, such as idiopathic interstitial lung disease.^{52,53} Potential therapeutic strategies focus on inhibiting PAFr or disrupting bacteria-choline phosphoryl interactions. Reported PAFr inhibitors are summarized in [Table 3](#), highlighting their potential in mitigating pathogen adhesion and progression of COPD.

Table 1 Risk Factors of COPD and AECOPD

Etiology	Triggers	Prevalence Rate	Impact	References
Viral Infection	<i>Influenza, Picornavirus, Respiratory Syncytial Virus, Coronaviruses, Parainfluenza, Adenovirus, Human Metapneumovirus</i>	34%	Deterioration of lung function, prolonged hospital stay, and more severe clinical course and worse hypoxaemia	[14–19]
Bacterial infection	<i>Pseudomonas aeruginosa, Klebsiella pneumoniae and Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae</i>	26% to 81%	Co-infection with viruses, 9% to 19% prevalence, leading to worse clinical outcomes	[20–22]
Outdoor pollutants	Sulphur dioxide (SO ₂), Nitrogen dioxide (NO ₂), Ozone (O ₃), carbon monoxide (CO), Small-diameter particulate matter (PM) _{2.5} , PM _{10/2.5} and coarse PM (2.5–10- μ m aerodynamic diameter)	4% to 38%	Significant decline in mortality with reduced SO ₂ and mixed effects of CO exposure on hospitalization rates	[23,24]
Indoor pollutants	Second-hand smoking and biomass fuel		Increased risk of emergency department visits and hospitalizations due to second-hand smoke exposure	[25,26]
Meteorological effect	Lower ambient temperatures (even 1°C drop), significant temperature drops (5°C), winter season, low humidity		Increased risk of AECOPD and hospital admissions, with lag effect up to 14 days	[27]

Table 2 List of Conventional Therapies Used to Treat COPD and AECOPD

Therapy	Usage	Delivery Route	Optimal Dosage	Key Outcomes	Limitations	References
Bronchodilators	SABA and short-acting anticholinergics used as initial treatment	MDI and nebulizer	Not specified	Show improvement in FEV1 and FVC with indacaterol, but some oxygen desaturation observed.No definitive evidence to favor one mode of delivery over another	No significant data available	[28–30]
Steroids	Used in severe AECOPD	Oral and Intravenous	Optimal dose (prednisone 40 mg daily) and duration (5 days)	Short-term steroid treatment (5 days) as effective as longer duration (14 days)	Oral steroids associated with fewer systemic effects compared to intravenous	[31,32]
Antibiotics	Used in AECOPD with sputum purulence and severe cases	Oral and Intravenous	Recommended duration of 5 to 7 days	Reduction in mortality, treatment failures, and hospital stay in ICU patients.Effective in reducing treatment failures, especially in ICU settings	Procalcitonin-guided therapy reduces antibiotic use and side effects	[33,34]
Pulmonary rehabilitation	For all patients with AECOPD	Structured and supervised programs	Duration, 6–12 weeks; Sessions, 36; Session timing, 1–2 hours	Reduces treatment failure, length of hospital stay, and improves lung function and breathlessness.		[35]
Oxygen Therapy	For hospitalized AECOPD			Titrated oxygen treatment recommended to lower risk of death, respiratory acidosis, and hypercapnia. Blood gases should be monitored to maintain PaO ₂ at 7.3–10 kPa (SaO ₂ 85–92%).The Free O ₂ device can improve target SaO ₂ maintenance and reduce hospital stay length.		[36]
High Flow Nasal Cannula (HFNC)	Used during severe hypoxemic acute respiratory failure (ARF).			HFNC delivers high FiO ₂ with positive pressure and nasopharyngeal dead space washout. Improves oxygenation, breathing pattern, and reduces work of breathing. Safe for stable hypercapnic patients. Recent studies show similar intubation and mortality rates compared to conventional oxygen therapy and NIMV. Limited evidence for efficacy in ICU patients.		[37,38]

Non-Invasive Mechanical Ventilation (NIMV)	Used for hypercapnic ARF with respiratory acidosis in AECOPD patients.			Strongly recommended for acute or acute-on-chronic respiratory acidosis (pH \leq 7.35). Minimizes risks, complications, duration of hospital stay, and intubation necessity. Cost-effective strategy. New helmet interface and helium/oxygen mixture may improve tolerance and gas exchange. Diaphragmatic dysfunction evaluation can predict NIMV failure and prognosis.		[39–41]
Dupilumab	Monoclonal antibody targeting IL-4/IL-13 pathways; reduces airway inflammation in eosinophilic COPD	Subcutaneous	300 mg every 2 weeks (common clinical dosage, but trials may vary)	Promotes quality of life, lowers the frequency of exacerbations in individuals with eosinophilic COPD, and improves lung function.	Costly, has systemic side effects, including injection site responses	[42,43]
Enfentrine	Dual inhibitor of PDE3 and PDE4; provides bronchodilation and anti-inflammatory effects	Inhalation (nebulizer)	3 mg twice daily via nebulizer	FEV1 significantly improved, symptoms were relieved, and the frequency of exacerbations in moderate-to-severe COPD decreased.	Long-term use is necessary for long-lasting benefits	[44]

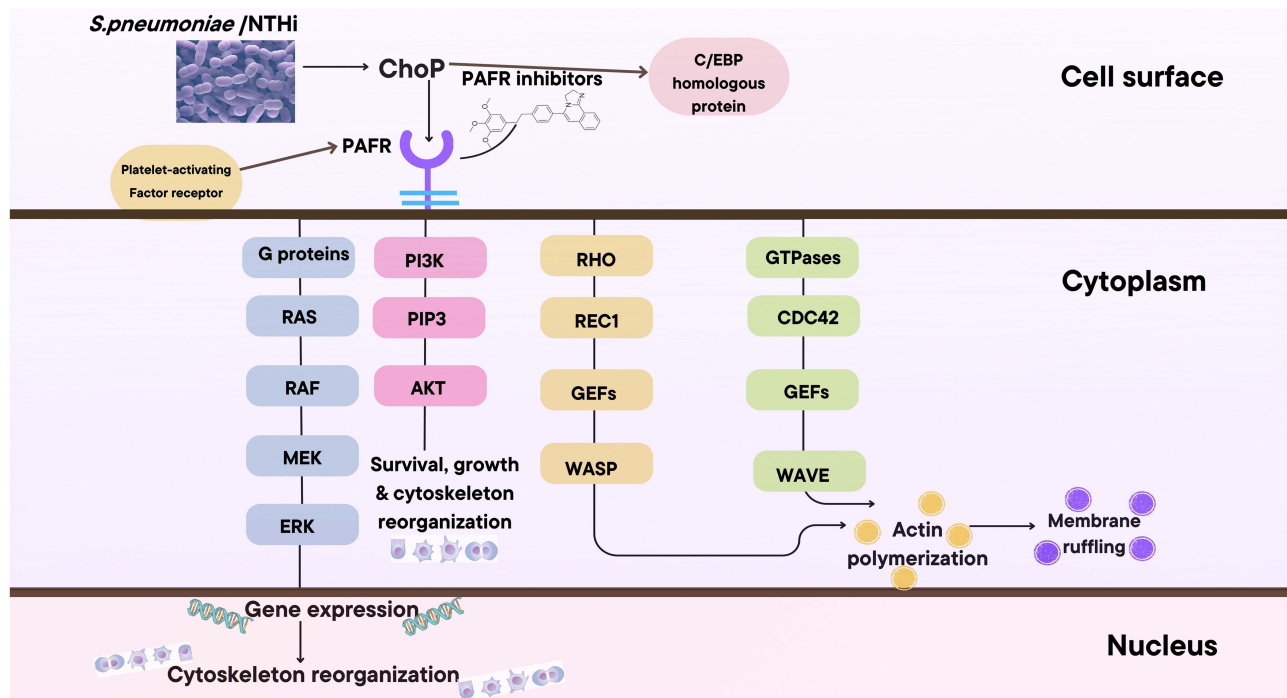


Figure 1 Platelet activating factor receptor (PAFr) inhibition as therapeutic approach for COPD.

Abbreviations, ANTHi, nontypeable *Haemophilus Influenza*; ChoP, phosphorylcholine; Ras, rat sarcoma, Raf, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; PI3K, Phosphoinositide 3-kinases; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; Akt, protein kinase B; Rho, guanine nucleotide-binding proteins; Rec1, recombination protein I; GEFs, guanine nucleotide exchange factors; WASP, Wiskott-Aldrich syndrome protein; cdc42, cell division cycle protein; WAVE, WASP-family verprolin-homologous protein.

Intracellular Adhesion Molecule-1 (ICAM-1)

The transmembrane glycoprotein ICAM-1, also referred to as CD54, plays a significant role in humans. ICAM-1 is continuously expressed across multiple cell types, including endothelial cells, respiratory epithelial cells, and leukocytes.⁵⁴ From a physiological perspective, ICAM-1 is critical for maintaining cell-to-cell interactions and facilitates the movement of white blood cells from the bloodstream into inflamed tissues, potentially triggering targeted immune responses to antigens.⁵⁵ ICAM-1 supports T-cell-mediated host defense by activating cytotoxic T cells in association with MHC class I, and on antigen-presenting cells, it activates MHC class II-restricted T cells through co-stimulatory molecules.⁵⁶

Table 3 Non-Eosinophilic Immunological Targets for COPD and AECOPD

Targets	Drug/Compound	Nature of drug	Mechanism	Therapy For	Developmental Stage	References
PAFr	CV-3988	—	Reduces bacterial adherence	COPD	Pre-clinical	[63]
	WEB-2086	—	Inhibits inflammatory pathways	COPD	Pre-clinical	[64]
	Simvastatin	Statin	Reduces PAFr expression and decreases bacterial load after pneumococcal infections	COPD	Approved for other indications	[65]
	Safflower yellow	Chinese herb	Affective for AECOPD treatment	AECOPD	Limited clinical evidence	[66,67]
	SR27417	—	Inhibits inflammatory pathways	COPD	Pre-clinical	[47]

(Continued)

Table 3 (Continued).

Targets	Drug/Compound	Nature of drug	Mechanism	Therapy For	Developmental Stage	References
ICAM-1 antagonist (binds to domain I of human ICAM-1)	14C11	Mouse anti-human ICAM-1 antibody	Reduces inflammation, pro-inflammatory cytokine production, and viral loads	COPD	Pre-clinical	[68,69]
SA	–	Small peptides	Inhibits viral entry in cell	COPD	Pre-clinical	[70]
SA + EGFR	–	Monoclonal antibodies	Inhibits viral entry in cell + Downstream the signalling of EGFR	COPD	Pre-clinical	[71–74]
SA	–	Dendritic polymers	Inhibits viral entry in cell	COPD	Pre-clinical	[75]
TLR	Ulinastatin	Protease inhibitor	Suppress TLR signaling and inflammatory response	COPD	In vivo trials (Phase II)	[76]
	Sulforaphane	–	Reduces inflammatory response	COPD	Pre-clinical trials	[77,78]
	Bufei Yishen	Chinese herb	Inhibits TLR and reduces inflammatory response	COPD	In-vivo trials	[79]
TLR + PKC	Resveratrol	Polyphenol	Suppresses TLR response and reduces inflammatory response + Disrupt PKC-related pathways	COPD	Pre-clinical	[80,81]
PKC	Defensins	Antimicrobial peptides	Inhibits PKC	COPD	Pre-clinical	[82–84]
PI3K	Nemiralisib	PI3K δ inhibitor	Reduces inflammation and viral susceptibility	–	Phase II	[85]
EGFR	Fucoidan	Sulfated polysaccharide from algae	Enhances immune responses and prevent EGFR-mediated viral entry	–	Phase II	[86–88]
Macrophages	Roflumilast	PDE-4 inhibitor	Favors a more reparative M2 macrophage phenotype	–	Phase III	[89]
	–	Macrolides	Improve phagocytic function in alveolar macrophages	AECOPD	–	[90]
	–	Statins	Improve phagocytic function in alveolar macrophages	–	Pre-clinical	[91]
PDE3 and PDE4	Ensifentrine	–	Dual inhibition increases cAMP/cGMP levels, leading to bronchodilation and anti-inflammatory effects.	COPD & AECOPD	Approved (2024)	[92]

Abnormal levels of ICAM-1 are associated with conditions such as AIDS, cancer, and allergic asthma.⁵⁷ One mechanism by which human rhinovirus (HRV) attaches to airway/lung epithelial cells—accounting for over 60% of the primary HRV group—is through the upregulation and modification of surface ICAM-1. This upregulation can result from external factors, such as cigarette smoke, or from the virus itself.⁵⁸ Paradoxically, increased ICAM-1 expression

appears to elevate susceptibility to viral infections. However, several bacterial and parasitic pathogens, including *Haemophilus influenzae* (NTHi) and *Plasmodium falciparum*, also utilize ICAM-1 to attach to and invade host cells.⁵⁹ For example, a controlled study showed that treating pulmonary epithelial cells with NTHi led to a fourfold increase in ICAM-1 expression⁶⁰ and a TNF-dependent rise in HRV39 binding.⁶¹ This finding suggests a mechanism for the exacerbated effects of bacterial and viral co-infections, offering insight into why COPD patients are especially vulnerable to combined infections with NTHi and HRV.⁶²

ICAM-1 is critical for the binding of NTHi and up to 90% of HRV serotypes to bronchial and alveolar epithelial cells.⁴⁸ When HRV's canyon protein binds to the ICAM-1 receptor, it triggers inflammatory mediators—TNF- α , IL-1 β , and IFN- γ —resulting in cell inflammation (Figure 2). Further data is needed to determine the frequency of NTHi utilizing this adhesion mechanism. The example of ICAM-1 inhibitor is enlisted in Table 3.

Sialic Acid (SA)

Sialic acids (SAs) are a group of nine-carbon monosaccharides prominently located on the outer surface of mammalian cells, particularly on glycoproteins within the cell membrane. These residues play a pivotal role in numerous biological processes, including the stabilization of glycoproteins and cellular membranes, as well as facilitating cell-cell recognition and interactions.⁹³ Elevated levels of SA have been observed by Bel'skaya et al⁹⁴ in both the blood and saliva of individuals with COPD, indicating a potential link to disease progression.

In terms of viral infection, influenza viruses primarily utilize sialic acid residues to enter bronchoepithelial cells (BECs). The viral hemagglutinin protein (HA-A) binds specifically to glycoproteins terminated with SA residues on host cells, particularly targeting SA α 2,6Gal and SA α 2,3Gal residues found on surface and inner respiratory epithelial cells. These residues serve as attachment points for human and avian influenza viruses.⁹⁵ Following attachment, the virus is taken into the cell via endocytosis and encapsulated in an endosome. The acidic environment within the endosome induces a conformational change in the viral

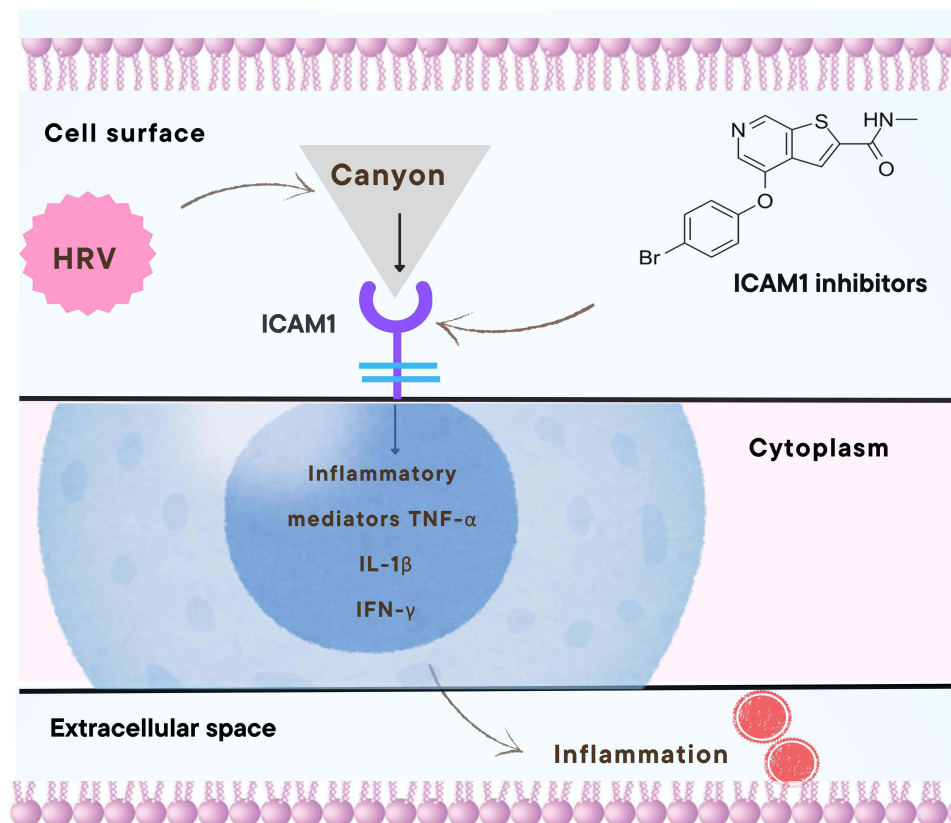


Figure 2 Intracellular adhesion molecule-I (ICAM-1) inhibition as therapeutic approach for COPD.

Abbreviations, HRV, human rhinovirus; TNF- α , tumor necrosis factor- α ; IL-1 β , Interleukin 1 β ; IFN- γ , Interferon γ .

HA-A protein, facilitating fusion with the endosomal membrane and subsequent release of viral genes into the host cytoplasm.⁹⁶ Upon contact with SA receptors, the influenza virus activates protein kinase C (PKC) and protein kinase R (PKR), which subsequently activate multiple inflammatory pathways. PKC activates the MEK/ERK and PI3K pathways, while PKR triggers the MAPK, IKK, and IPS-1 pathways, ultimately resulting in cell reorganization and inflammation through the activation of c-Jun, NF- κ B, and IRF3⁹⁷ (Figure 3). Some reported SA inhibitors are enlisted in Table 3.

TLR-Mediated Response

The disruption of macrophage responses via Toll-like receptors (TLRs) plays a critical role in the development and progression of chronic obstructive pulmonary disease (COPD).⁹⁸ Research suggests that chronic bacterial colonization or infection, combined with exposure to cigarette smoke, can overstimulate the immune system through TLRs, leading to inflammation and subsequent airway remodeling and lung tissue damage⁹⁹ (Figure 4). In COPD patients, TLR activation, particularly through TLR3, TLR7, and TLR8 in response to viral triggers, has been associated with elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and CTLA-5.¹⁰⁰ Additionally, TLR4 activation, followed by TLR2 activation in alveolar macrophages, contributes to increased cytokine production.⁹⁸

TLR2 and TLR4 are especially crucial for recognizing Gram-positive and Gram-negative bacteria's pathogen-associated molecular patterns (PAMPs), respectively.¹⁰¹ Upon ligand binding, TLR2 and TLR4 initiate a MyD88-dependent signaling pathway that activates the mitogen-activated protein kinase (MAPK) cascade and nuclear factor- κ B (NF- κ B), leading to the release of pro-inflammatory mediators.¹⁰² This MyD88 pathway is central to TLR signal transduction.¹⁰⁰ COPD patients frequently have bacterial colonization of the lower airways with pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.^{103–105} Some reported TLR inhibitors are enlisted in Table 3.

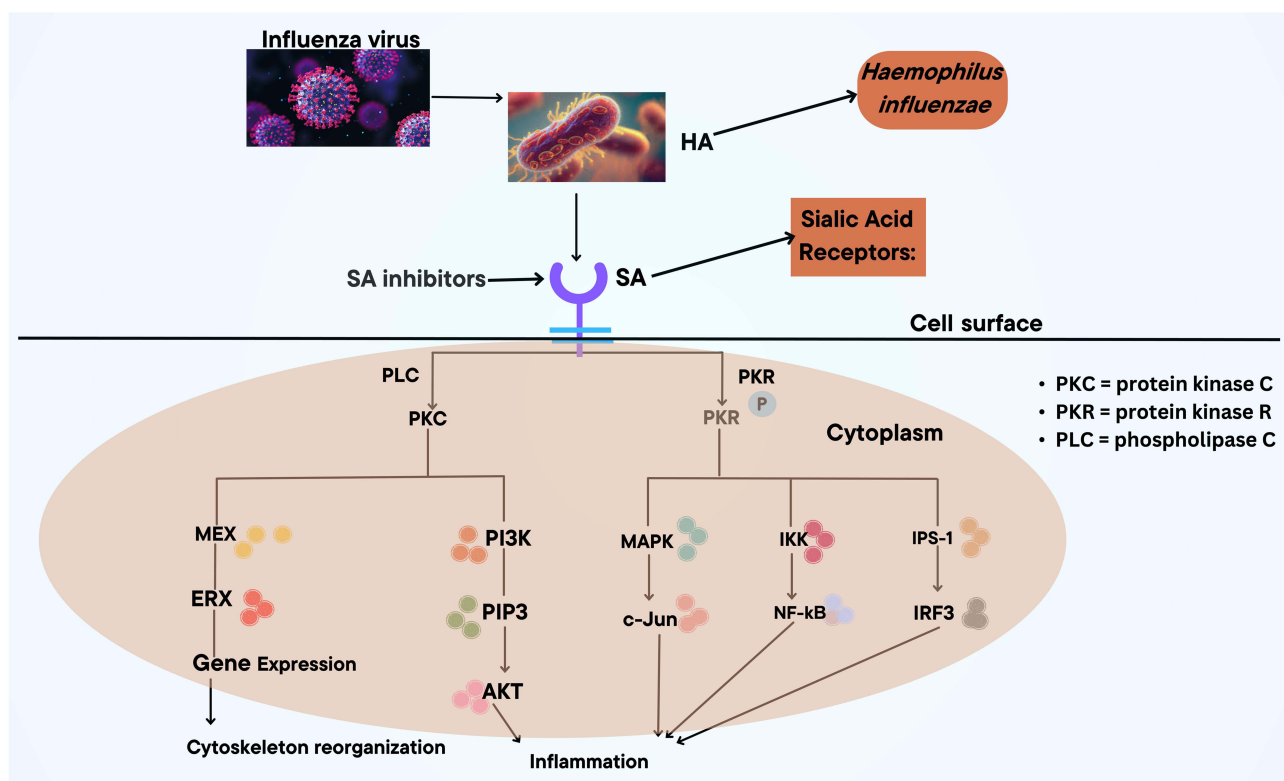


Figure 3 Sialic acid (SA) inhibition as therapeutic approach for COPD.

Abbreviations: HA, Hemagglutinin; PLC, phospholipase C; PKC, Protein kinase C; ERK, extracellular signal regulated kinase; PKR, Protein kinase R; PKR-P, Protein kinase R-phosphorylated; MAPK, Mitogen activated protein kinase; IKK, I κ B kinase; IPS-1, Interferon- β Promoter Stimulator 1; c-Jun, A component of the activator protein 1; NF- κ B, Nuclear factor kappa B; IRF3, Interferon regulatory factor 3.

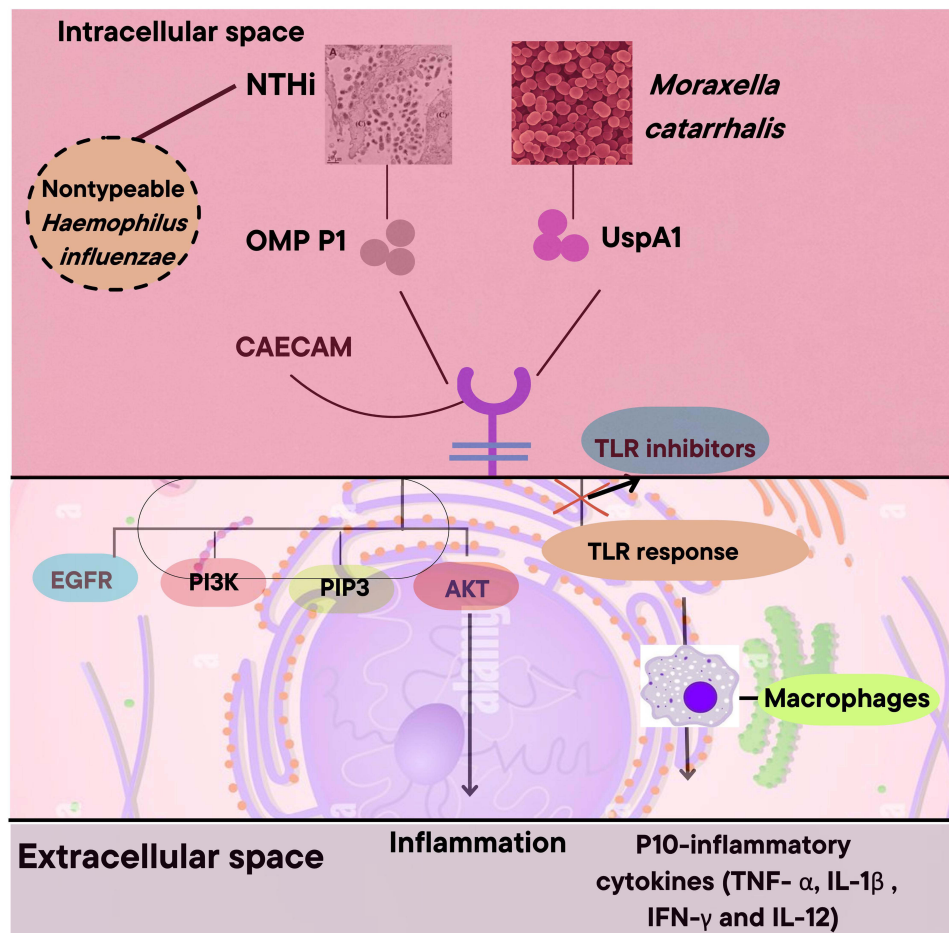


Figure 4 TLR inhibition as therapeutic approach for COPD.

Abbreviations: NTHi, nontypeable *Haemophilus Influenzae*; OMP P1, Outer membrane protein P1; UspA1, Ubiquitous surface protein A1; EGFR, Epidermal growth factor receptor; TLR, Toll-like receptor; IL-1 β , Interleukin 1 β ; IFN- γ , Interferon γ ; TNF, tumor necrosis factor; IL-12, Interleukin 12.

Enzymes/Proteins

Phosphodiesterase (PDE)3 and PDE4

Inhibitors of phosphodiesterase (PDE)3 and PDE4 play a crucial role in managing various respiratory functions.¹⁰⁶ PDE3 is responsible for regulating the levels of cyclic AMP (cAMP) and cyclic GMP (cGMP) in airway smooth muscle, which directly influences bronchial tone.¹⁰⁷ On the other hand, PDE4 primarily regulates cAMP and is involved in the activation and migration of inflammatory cells, as well as stimulating the cystic fibrosis transmembrane conductance regulator in bronchial epithelial cells.¹⁰⁸

The dual inhibition of both PDE3 and PDE4 has demonstrated enhanced or synergistic effects compared to targeting either enzyme alone. This combined approach improves airway smooth muscle contraction and reduces inflammatory responses, making it a promising strategy for treating obstructive and inflammatory respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis, and asthma.^{109,110}

Protein Kinase C (PKC)

The protein kinase C (PKC) superfamily plays a central role in numerous signaling pathways, influencing processes such as membrane dynamics, immune responses, gene expression, and cell growth.¹¹¹ PKCs are particularly important in viral infections, as influenza viruses and their hemagglutinin (HA) proteins can rapidly activate PKC enzymes upon binding to host cell receptors.¹¹² Experimental studies have shown that inhibiting PKCs can impair viral entry and infectivity in enveloped viruses, including influenza A and B, underscoring the role of PKC in viral cell entry.¹¹³ Specifically, PKC

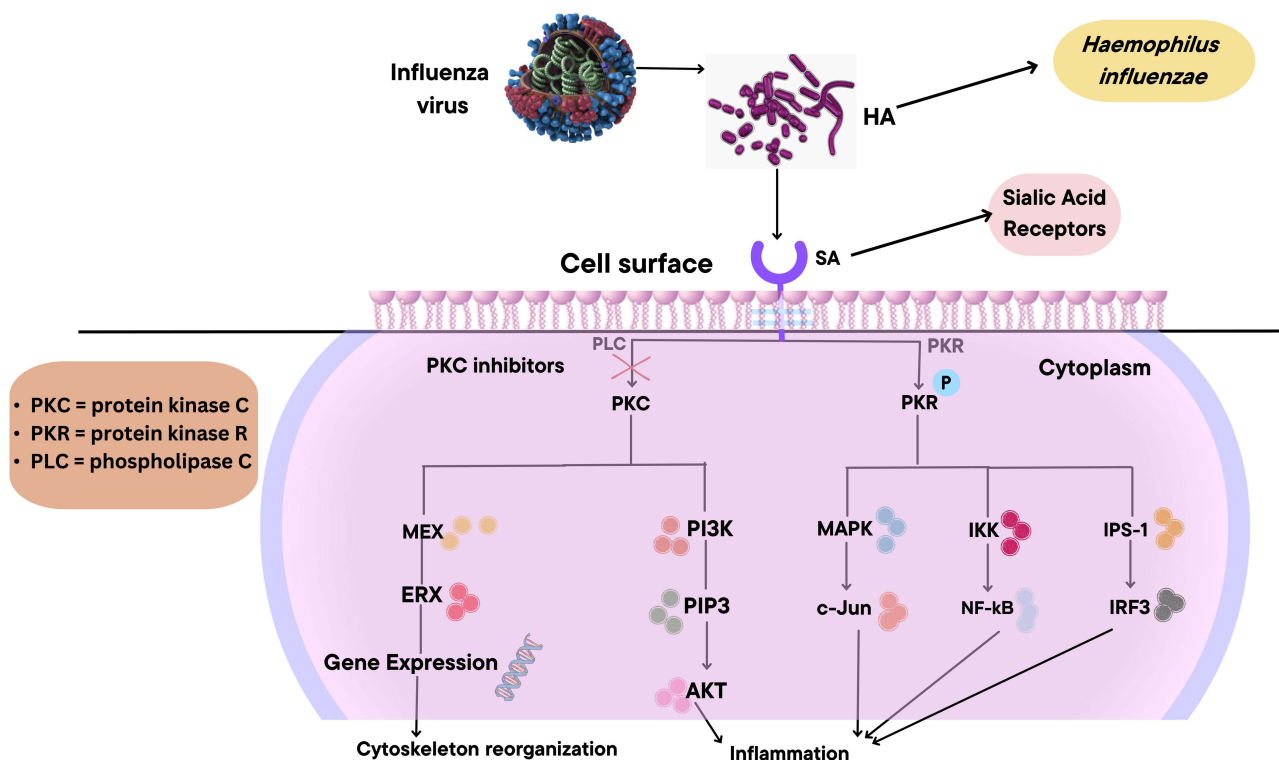


Figure 5 Protein kinase C Inhibition as therapeutic approach for COPD.

activation leads to the stimulation of the MEK/ERK and PI3K pathways, promoting cytoskeletal reorganization and inflammation, which support viral entry (Figure 5).

Although the precise mechanisms by which PKCs facilitate viral entry are not fully understood, PKC β II isoform appears to be critical for the late endosomal sorting required for influenza virus entry.¹¹⁴ PKC activation by respiratory syncytial virus (RSV) in A549 lung epithelial cells has also been shown to increase expression of several PKC isoforms, activating extracellular signal-regulated kinases essential for cell fusion and infection.¹¹⁵ Inhibitory drugs administered early in infection significantly blocked RSV infection in NHBE cells by targeting PKC, suggesting that pharmacological PKC inhibition may be a viable strategy for controlling influenza and RSV by preventing virions from entering host cells¹¹⁶ (Table 3).

Phosphoinositide 3-Kinase (PI3K)

The influenza virus's non-structural protein 1 (NS1) directly interacts with the p85 subunit of phosphoinositide 3-kinase (PI3K), leading to the activation of PI3K and downstream Akt signaling.^{117,118} PI3K plays a vital role in cellular processes like inhibiting apoptosis, promoting cell growth, regulating metabolism, and initiating cytokine production (Figure 6).¹¹⁹ Several investigations have linked PI3K in facilitating effective viral proliferation.¹²⁰ PI3K's activation has been linked to enhanced viral proliferation, as it facilitates virus entry, viral RNA synthesis, protein production, and the prevention of premature cell death, all of which are critical for effective viral replication.¹²¹

Individuals with COPD exhibit hyper-expression of PI3K in lung tissues, a factor that increases their vulnerability to viral infections and may contribute to the disease's progression.^{85,122} The severity of airflow obstruction in COPD patients has been correlated with elevated PI3K levels and decreased levels of PTEN, a negative regulator of the PI3K pathway.¹²³ Cigarette smoke extract (CSE) further exacerbates this effect by reducing PTEN expression in bronchial epithelial cells, leading to increased Akt phosphorylation and the release of proinflammatory cytokines.^{124,125}

Studies have identified PI3K isoforms that are particularly implicated in COPD pathology. The PI3K-p110 α isoform is notably overexpressed in primary bronchial epithelial cells (pBECs) from COPD patients. Reducing p110 α expression prior to infection has been shown to decrease viral effects and enhance the antiviral response mediated by IFN- β ,

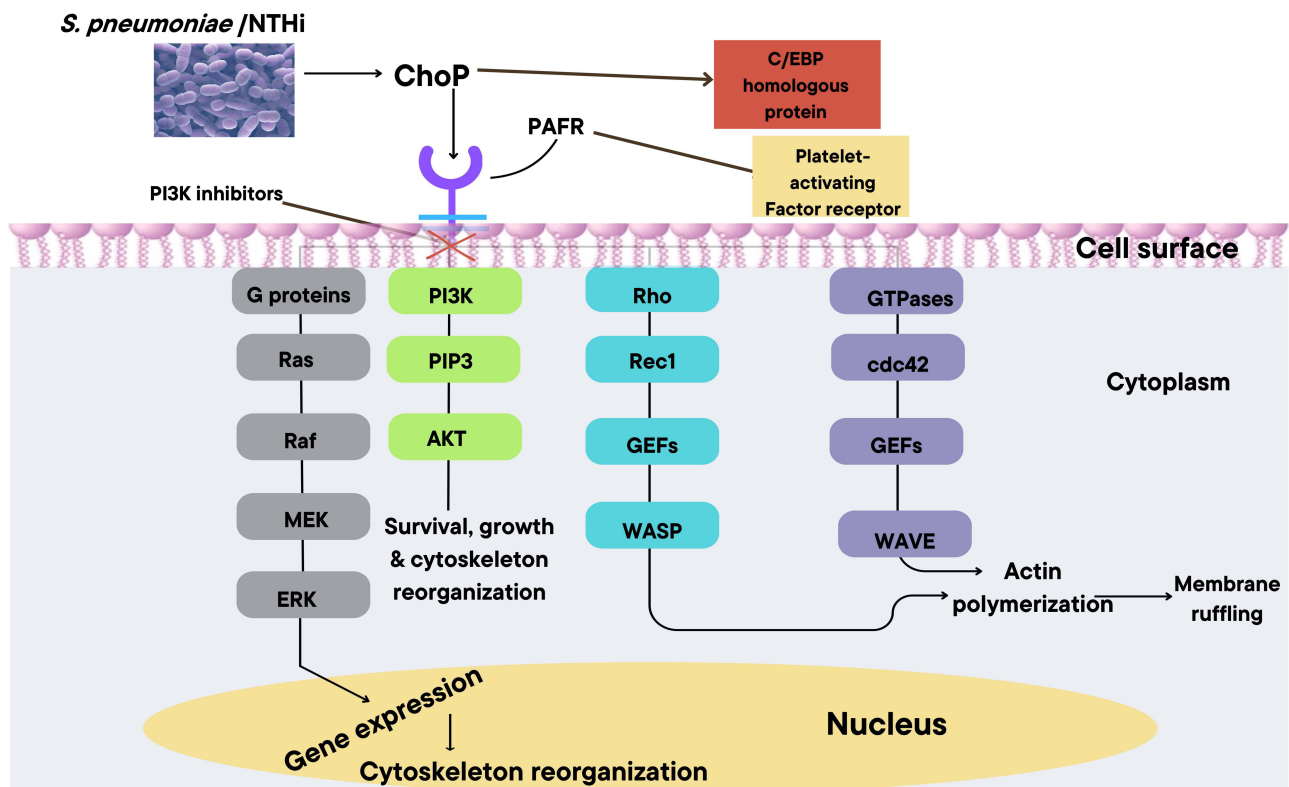


Figure 6 Phosphoinositide 3-kinase inhibition as therapeutic approach for COPD.

particularly in healthy and COPD-affected primary bronchial cells.¹²⁶ This isoform-specific targeting could enable the development of selective inhibitors that minimize unintended effects. Another PI3K isoform, PI3K γ , which is primarily expressed in hematopoietic cells, plays a role in immune responses to viral infections, although its involvement in COPD remains unexplored.¹²⁷ Example is enlisted in Table 3.

Epidermal Growth Factor Receptor (EGFR)

The epidermal growth factor receptor (EGFR), a receptor kinase, plays a key role in tissue repair, mucin synthesis, and IL-8 production in lung epithelial cells, particularly in response to elastase.¹²⁸ Viral infections, including those caused by influenza and human rhinovirus (HRV), have been shown to enhance EGFR activation and IL-8 production in bronchial epithelial cells, contributing to increased viral adherence to airway tissues.¹²⁹ Research suggests that EGFR facilitates influenza A virus infection via the PI3K/Akt signaling pathway, indirectly promoting viral proliferation.¹³⁰

Chronic EGFR activation, whether due to viral infections or impaired antioxidant defense in COPD, can lead to airway remodeling and subsequent airway narrowing—a key pathological feature of COPD.¹³¹ EGFR also supports the antiviral response mediated by interferon (IFN), although viral infections like influenza A and HRV can suppress IFN- γ production, increasing viral replication in bronchial cells.^{58,132} Blocking EGFR has been shown to enhance IFN- γ levels and reduce viral load in both in vitro and in vivo studies, highlighting EGFR inhibition as a promising antiviral strategy.

In addition to its role in viral infections, EGFR activation is also stimulated by bacteria like *Moraxella catarrhalis*, which commonly exacerbates COPD symptoms.^{133,134} EGFR inhibition may therefore offer a dual benefit, reducing COPD exacerbations from bacterial and viral sources while addressing the underlying disease mechanisms (Table 3).

ST β -Galactoside Alpha-2,6-Sialyltransferase I (ST6GAL1)

Glycosylation, the attachment of sugar molecules to proteins and lipids, plays an essential role in regulating various cellular processes in eukaryotic cells, affecting both physiological and pathological states.¹³⁵ One key glycosylation enzyme, ST6GAL1, is a type II membrane protein localized mainly in the Golgi apparatus and is responsible for

transferring sialic acid from CMP-sialic acid to galactose-containing glycans.^{136,137} Through this sialylation, ST6GAL1 influences critical molecular pathways, including Notch1, Hes1, MMPs, and VEGF, which are known to play a role in lung cancer progression. Alterations in α 2-6 sialylation have been specifically implicated in promoting lung cancer, highlighting ST6GAL1's importance in cancer-related pathways.¹³⁸

In the context of respiratory diseases, ST6GAL1 has been associated with airway mucin regulation and changes in sialylation levels in asthma, contributing to altered cell proliferation and inflammation.¹³⁹ However, studies on ST6GAL1's role in other chronic lung disorders remain limited, and its exact functions within these conditions are not yet fully understood.

Krick et al¹⁴⁰ explored ST6GAL1's role in inflammation by examining its effects on IL-6 production in human bronchial epithelial cells (HBECs). They found that ST6GAL1 deficiency led to elevated IL-6 production and release. Exposure to cigarette smoke medium or extract (CSE), as well as inhibition of BACE1, further suppressed ST6GAL1 secretion, reduced α 2-6 sialylation, and increased IL-6 levels in HBECs. This relationship between ST6GAL1 and IL-6 suggests that decreased ST6GAL1 levels, with subsequent α 2-6 sialylation reduction, might exacerbate inflammation in the lungs.

Additionally, a study on a small group of COPD patients revealed that lower plasma ST6GAL1 levels were correlated with a higher risk of future acute exacerbations of COPD (AECOPD), whereas IL-6 levels showed a positive correlation with exacerbation risk. These findings suggest that reduced ST6GAL1 and α 2-6 sialylation levels may contribute to worse clinical outcomes in COPD through heightened inflammation, specifically by increasing IL-6 levels. This insight points to ST6GAL1 and α 2-6 sialylation as potential biomarkers and therapeutic targets for managing inflammation in COPD and possibly other chronic lung diseases.

Annexin-1

Annexin A1, a polyunsaturated fatty acid-containing molecule, plays a crucial role in resolving neutrophilic inflammation by enhancing efferocytosis, the process through which dying neutrophils are cleared, and by inhibiting further recruitment of neutrophils.¹⁴¹ As a pro-resolving molecule, annexin A1 is increasingly viewed as a therapeutic target, particularly due to its roles in inflammation and in infections, such as those caused by *nontypeable Haemophilus influenzae* (NTHi).¹⁴² Interestingly, while increased levels of annexin A1 facilitate influenza virus binding, replication, and nuclear translocation from endosomes, mice lacking annexin A1 have demonstrated increased survival rates and reduced viral loads during influenza A infections, alongside a rise in inflammatory cell infiltration.¹⁴³

In the context of COPD, annexin A1 has shown variable associations with disease severity. Higher serum levels of annexin A1 have been linked to more severe cases of COPD, suggesting an impaired inflammation-resolving capacity within the chronic inflammatory environment typical of the disease. Similarly, increased or dysfunctional pro-resolving mediator levels have also been noted in conditions like inflammatory bowel syndrome, preeclampsia, and Alzheimer's disease, suggesting that a common pathway involving dysfunctional inflammation resolution may be at play across these chronic conditions.¹⁴⁴

However, another study involving a larger participant pool found that serum annexin A1 levels were lower in COPD patients compared to healthy non-smokers. Both studies agree, though, that annexin A1 expression in human bronchial epithelial (HBE) cells increases in response to cigarette smoke extract (CSE), and this expression correlates with COPD severity.¹⁴⁵ The discrepancy between these studies remains unexplained but could relate to sample variation, underscoring the need for further research to clarify annexin A1's role in COPD.

Modulating pro-resolution molecules like annexin A1 offers potential therapeutic benefits, including slowing COPD progression, reducing airway wall thickness, and preventing virus-induced exacerbations.¹⁴⁶ Such interventions might also prove beneficial for other lung conditions marked by reduced macrophage-mediated efferocytosis, such as cystic fibrosis (CF) and interstitial pulmonary fibrosis (IPF).¹⁴⁷ This potential highlights the need to investigate annexin A1 and similar molecules as part of targeted therapies for inflammatory lung diseases.

Immune Cells

Macrophages

Macrophages are essential for lung defense against pathogens, utilizing Toll-like receptors (TLRs) to recognize pathogen-associated molecular patterns (PAMPs).¹⁴⁸ Lung macrophages adapt by modulating their functions and phenotypes in response to diverse stimuli,¹⁴⁹ with two main types involved, classically activated M1 and alternatively activated M2 macrophages.¹⁵⁰ M1 macrophages respond to bacterial antigens and IFN- γ by enhancing Th1 immunity and releasing pro-inflammatory cytokines, including IL-1 β , TNF, and IL-12, to eliminate pathogens.¹⁵¹

M1 macrophages also produce reactive nitrogen and oxygen species, which have bactericidal effects but can be toxic to host tissues.¹⁵² M2 macrophages counterbalance these effects, promoting tissue repair, fibrosis, and efferocytosis by releasing regulatory cytokines like IL-10 and TGF- β , often in response to stimuli like IL-4, IL-13, and apoptotic cells (Figure 7).¹⁵³ This duality is essential for balanced immune responses but becomes dysregulated in chronic lung diseases like COPD.

In COPD, macrophage numbers increase, but their ability to clear pathogens and dead cells decreases, indicating a functional deficit.^{154,155} COPD-related airway macrophages shift towards an M1-dominated airway wall and an M2-polarized airway lumen, contributing to the chronic inflammatory environment typical of the disease.¹⁵⁶ This shift may be an adaptive response to continuous insult from cigarette smoke and microbial colonization.¹⁵⁷

One mechanism involved in this macrophage imbalance is the competition between iNOS (M1 marker) and arginase-1 (M2 marker), both of which utilize arginine. Elevated arginase-1 in COPD macrophages inhibits iNOS, compromising antimicrobial activity and encouraging collagen deposition, thereby promoting airway remodeling and infection susceptibility.¹⁵⁸ Additionally, the phagocytic and efferocytic functions of macrophages are impaired in COPD, exacerbated by smoking, which reduces these functions even in healthy smokers.^{159,160} Some reported macrophage inhibitors are enlisted in Table 3.

Others

Oxidative Stress

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) play essential roles in the immune response against pathogens. While they exhibit antimicrobial activity, their excessive accumulation or inadequate removal—due to impaired antioxidant defenses—leads to oxidative damage, impacting DNA, lipids, and proteins.¹⁶¹ Chronic oxidative stress, a hallmark of COPD, contributes significantly to airway damage, with ROS production sustained even after smoking cessation, suggesting additional endogenous factors like persistent infection or pathogens in ROS accumulation.^{162,163}

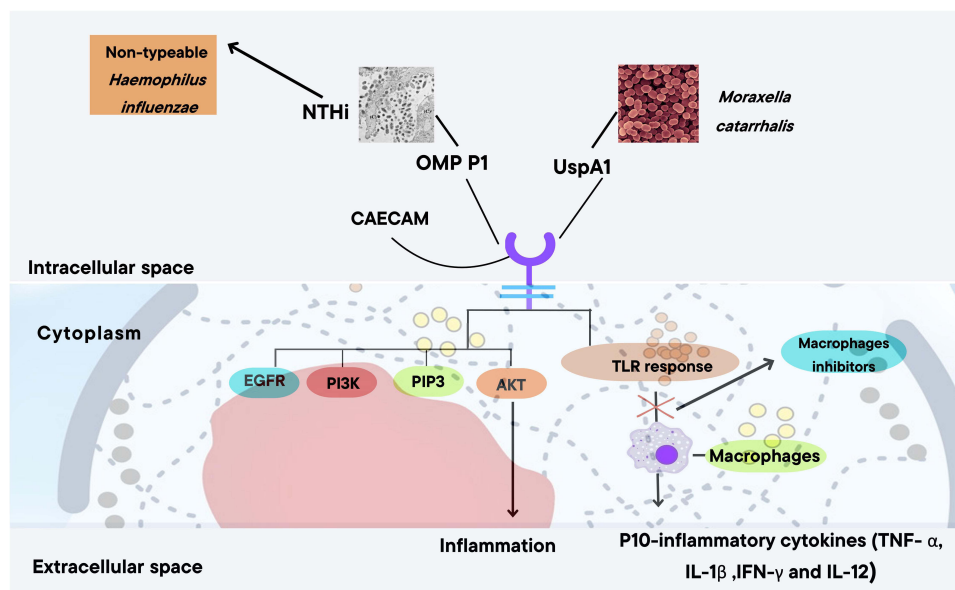


Figure 7 Macrophage Inhibition as therapeutic approach for COPD.

In COPD models, ROS generation intensifies in response to bacterial and viral attacks.¹⁶⁴ Although ROS has a protective role, excessive levels compromise phagocytosis and efferocytosis, reducing pathogen clearance and perpetuating an overactive ROS response.¹⁶⁵ Targeting this oxidative load in COPD could involve enhancing antioxidant enzyme activity or inhibiting ROS-producing enzymes like NADPH oxidases (NOX).¹⁶⁶

The NOX2 isoform, primarily responsible for ROS production in inflammatory cells, is pivotal for ROS generation directed against bacterial and fungal invaders.¹⁶⁷ Yet, studies suggest NOX2 activation might exacerbate viral infections, as seen with influenza A virus, where NOX2 absence led to reduced lung inflammation and viral load in mice.¹⁶⁸ These findings underscore NOX2's role in COPD, where its increased gene expression correlates with airway inflammation.¹⁶⁹ Inhibiting NOX2 with compounds like apocynin has shown efficacy in lowering airway inflammation, viral titers, and ROS levels in COPD mouse models,^{170,171} although immunosuppressive risks remain a concern.¹⁷²

Other NOX isoforms may also influence COPD progression. For example, NOX4, activated by cigarette smoke, may contribute to airway remodeling in small airways.^{153,173} Consequently, selective targeting of NOX isoforms could optimize therapeutic efficacy and reduce ROS production in COPD patients.

Enhancing antioxidant enzyme activity, particularly through glutathione peroxidase (Gpx) and superoxide dismutase (SOD) modifications, represents another approach to reduce oxidative stress in COPD. These enzymes neutralize superoxide radicals, primarily generated during cellular respiration.¹⁷⁴ Gpx1, found extensively in lung tissues, and extracellular SOD (SOD3) have demonstrated protective effects in animal COPD models. Gpx and SOD mimetics, including ebselen, have shown promising effects in reducing inflammation and protecting lung tissue during viral infections like influenza.¹⁷⁵ Interestingly, genetic variations in SOD3 have been linked to COPD susceptibility, with certain SOD3 mutations providing protective effects, particularly in smokers.^{164,166,176} While reducing ROS production or boosting antioxidant capacity could theoretically alleviate COPD exacerbations and progression, research on these interventions' efficacy and safety in humans remains limited. By clarifying ROS's role in viral pathogenicity and COPD development, we can potentially devise effective, comprehensive treatments for COPD management.

Iron

Recent research has revealed a concerning link between iron accumulation in the lungs and the progression of pulmonary disorders, particularly pulmonary fibrosis, asthma, and COPD. Studies have found a correlation between elevated iron levels in the lungs and increased airflow obstruction and emphysema severity, suggesting that iron is a key factor in COPD pathology. Proteomic and genome-wide association studies (GWAS) also support the involvement of iron-related genes in worsening airway symptoms, further establishing this association.^{177,178}

Experiments using animal models have shown that chelation therapy, which removes free iron, can alleviate cigarette smoke-induced emphysema. This finding suggests that iron contributes to COPD susceptibility, potentially by fostering bacterial colonization and infection in the airways. Supporting this, cell-line studies indicate that iron overload can lead to lysosomal dysfunction and reduced bacterial killing capability. In experimental settings, the bactericidal function of murine alveolar macrophages was enhanced when iron was chelated, pointing to a direct influence of iron on immune cell function.^{179,180}

Specifically, Ho et al¹⁷⁹ explored whether elevated iron in sputum macrophages could increase the risk of infective acute exacerbations in COPD (AECOPD). Both interleukin-6 (IL-6) and hepcidin are known to play roles in iron sequestration within the lungs. Their study provided *in vitro* and population-based evidence suggesting that excess iron in pulmonary macrophages might lead to recurrent infections in COPD patients. They hypothesize that IL-6-mediated iron sequestration within sputum macrophages could impair immune cell function, resulting in higher infection rates and worsening COPD symptoms. Overall, these findings underscore the importance of understanding iron metabolism in COPD and exploring therapeutic strategies like iron chelation to limit iron's adverse effects on airway health.

Conclusion

The optimal treatment of COPD continues to evolve, with a growing focus on therapies targeting specific molecular pathways involved in disease progression. While many biologics have been investigated, significant progress is still required to identify those that can effectively modify the disease and improve long-term outcomes. Current research

highlights the importance of targeting specific immune responses to enhance the efficacy of treatments while minimizing the side effects seen with traditional therapies.

In terms of clinical trials, the outcomes for assessing efficacy are well-established at various stages of development. Phase 3 trials use a clear set of accepted outcome measures that are recognized by regulatory bodies, including lung function, exacerbation rates, and quality of life assessments. In Phase 2 trials, carefully selected biomarkers and surrogate endpoints are frequently explored to gauge early efficacy. The inclusion criteria for clinical trials vary depending on the mechanism of action of the therapy under investigation, and these criteria should be tailored to specific patient populations to ensure the trials' relevance and validity.

Understanding the role of molecular and immunological targets in COPD pathology, as well as their influence on clinical outcomes, will guide the development of more effective and personalized treatments. Further research into biomarkers, the role of iron metabolism, and oxidative stress mechanisms will be key to refining treatment strategies and improving patient outcomes in COPD management.

Funding

This research was funded by the Science and Technology Development Plan Project of Jilin Province-Technology Innovation Guidance (Grant No. 20220401061YY), the Science and Technology Development Plan Project of Jilin Province-Key Research and Development (Grant No. 20230204055YY) and Norman Bethune Program of Jilin University (Grant No. 2023B34).

Disclosure

The authors declare no conflicts of interest in this work.

References

- Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan IJTLRM. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019, a systematic review and modelling analysis. *Lancet Respir Med.* 2022;10(5):447–458. doi:10.1016/S2213-2600(21)00511-7
- Halpin DRM. Mortality of patients with COPD. *Exp Rev Respir Med.* 2024;18(6):381–395. doi:10.1080/17476348.2024.2375416
- Al Wachami N, Guennouni M, Iderdar Y, et al. Estimating the global prevalence of chronic obstructive pulmonary disease (COPD), a systematic review and meta-analysis. *BMC Public Health.* 2024;24(1):297. doi:10.1186/s12889-024-17686-9
- Vogelmeier CF, Roman-Rodriguez M, Singh D, Han MK, Rodriguez-Roisin R, Ferguson G. Goals of COPD treatment, focus on symptoms and exacerbations. *Respiratory Medicine.* 2020;166:105938. doi:10.1016/j.rmed.2020.105938
- Prediletto I, Giancotti G, Nava CM. COPD Exacerbation, why it is important to avoid ICU admission. *J Clin Med.* 2023;12(10):3369. doi:10.3390/jcm12103369
- Schellack N, Truter A, Ntuli P, Mokwele N, Mogale K, Esterhuizen AJSPJ. A 2021 update, approach to asthma management in adults. *SA Pharm J* 2021;88(4):17–24.
- Rosenwasser Y, Berger I, Loewy ZGJP. Therapeutic approaches for chronic obstructive pulmonary disease (COPD) exacerbations. *Pathogens.* 2022;11(12):1513. doi:10.3390/pathogens11121513
- Linerós R, Fernández-Delgado L, Vega-Rioja A, et al. Associated factors of pneumonia in individuals with chronic obstructive pulmonary disease (COPD) apart from the use of inhaled corticosteroids. *Biomedicines.* 2023;11(5):1243. doi:10.3390/biomedicines11051243
- Muteeb G, Rehman MT, Shahwan M, Aatif MJP. Origin of antibiotics and antibiotic resistance, and their impacts on drug development, a narrative review. *Pharmaceuticals.* 2023;16(11):1615. doi:10.3390/ph16111615
- Chellappan DK, Prasher P, Shukla SD, et al. Exploring the role of antibiotics and steroids in managing respiratory diseases. *J Biochem Mol Toxicol.* 2022;36(10):e23174. doi:10.1002/jbt.23174
- Matera MG, Cazzola M, Page CJCOi P. Prospects for COPD treatment. *Curr Opin Pharmacol.* 2021;56:74–84. doi:10.1016/j.coph.2020.11.003
- Buhr RG, Jackson NJ, Dubinett SM, Kominski GF, Mangione CM, Ong M. Factors associated with differential readmission diagnoses following acute exacerbations of chronic obstructive pulmonary disease. *J Hosp Med.* 2020;15(4):219–227. doi:10.12788/jhm.3367
- Buttery SC, Zysman M, Vikjord SA, Hopkinson NS, Jenkins C, Vanfleteren LEJR. Contemporary perspectives in COPD, patient burden, the role of gender and trajectories of multimorbidity. *Respirology (Carlton, Vic.).* 2021;26(5):419–441. doi:10.1111/resp.14032
- Bénézit F, Loubet P, Galtier F, et al. Non-influenza respiratory viruses in adult patients admitted with influenza-like illness, a 3-year prospective multicenter study. *Infection.* 2020;48(4):489–495. doi:10.1007/s15010-019-01388-1
- D'Anna SE, Maniscalco M, Cappello F, et al. Bacterial and viral infections and related inflammatory responses in chronic obstructive pulmonary disease. *Annals of Medicine.* 2021;53(1):135–150. doi:10.1080/07853890.2020.1831050
- Liao K-M, Chen Y-J, Shen C-W, Ou S-K, Chen C-YCOPD. The influence of influenza virus infections in patients with chronic obstructive pulmonary disease. *Int J Chronic Obst Pulm Dis.* 2022;17:2253–2261. doi:10.2147/COPD.S378034
- Prasad N, Walker TA, Waite B, et al. Respiratory syncytial virus-associated hospitalizations among adults with chronic medical conditions. *Clinical Infectious Diseases, an Official Publication of the Infectious Diseases Society of America.* 2021;73(1):e158–e163. doi:10.1093/cid/ciaa730

18. Satia I, Cusack R, Greene JM, O'Byrne PM, Killian KJ, Johnston N. Prevalence and contribution of respiratory viruses in the community to rates of emergency department visits and hospitalizations with respiratory tract infections, chronic obstructive pulmonary disease and asthma. *PLoS One*. 2020;15(2):e0228544. doi:10.1371/journal.pone.0228544
19. Walter JM. *Other Respiratory Viruses as a Cause of Community-Acquired Pneumonia*. Thieme Medical Publishers; 2020:579–591.
20. Nagabhushan B. *A Prospective Study on Community Acquired Pneumonia With Special Reference to Its Etiology, Clinical Profile, Risk Factors, Complications, and Radiographic Features in Elder Age Group in a Tertiary Care Hospital*. Rajiv Gandhi University of Health Sciences (India); 2020.
21. Nguyen-Van T, Pham-Hung V, Tran-Van N, et al. Microbial characteristics of lower respiratory tract infections in patients referred from primary care hospitals. *J Health Sci Med Res* 2024;42(3):20231004.
22. Zhuo X, Zhao J, Wang L, et al. Development and evaluation of a multiplex quantitative polymerase chain reaction assay for detecting bacteria associated with lower respiratory tract infection. *Int J Infect Dis*. 2022;122:202–211. doi:10.1016/j.ijid.2022.05.052
23. Song J, Qiu W, Huang X, et al. Association of ambient carbon monoxide exposure with hospitalization risk for respiratory diseases, a time series study in Ganzhou, China. *Front Public Health*. 2023;11:1106336.
24. Orellano P, Reynoso J, Quaranta N. Short-term exposure to sulphur dioxide (SO₂) and all-cause and respiratory mortality, a systematic review and meta-analysis. *Environ Int*. 2021;150:106434.
25. Sharma R, Kurmi O, Hariprasad P, Tyagi SJJJo AE. Health implications due to exposure to fine and ultra-fine particulate matters, a short review. *Int J Ambient Energy*. 2024;45(1):2314256.
26. Pawankar R, Wang J-Y, Wang I-J, et al. Asia Pacific Association of allergy asthma and clinical immunology white paper 2020 on climate change, air pollution, and biodiversity in Asia-Pacific and impact on allergic diseases. *Asia Pacific Allergy*. 2020;10(1):e11. doi:10.5415/apallergy.2020.10.e11
27. Baniasad M, Mofrad MG, Bahmanabadi B, Jamshidi S. COVID-19 in Asia, transmission factors, re-opening policies, and vaccination simulation. *Environ Res*. 2021;202:111657. doi:10.1016/j.envres.2021.111657
28. Whittaker Brown S-A, Braman SS. *Pulmonary Disease. Geriatric Medicine, A Person Centered Evidence Based Approach*. Springer; 2023:1–26.
29. India LJLI. *Lung India*; 2013.
30. Al-Moamary MS, Alhaider SA, Alangari AA, et al. The Saudi initiative for asthma-2019 update, guidelines for the diagnosis and management of asthma in adults and children. *Ann ThoracMed*. 2019;14(1):3–48. doi:10.4103/atm.ATM_327_18
31. Sherry HY, Drucker AM, Lebwohl M, Silverberg JA. A systematic review of the safety and efficacy of systemic corticosteroids in atopic dermatitis. *J Am Acad Dermatol*. 2018;78(4):733–740.e11. doi:10.1016/j.jaad.2017.09.074
32. Williams D. Clinical pharmacology of corticosteroids. *Respir Care*. 2018;63(6):655–670.
33. Gupta N, Haley R, Gupta A, Sethi S. *Chronic Obstructive Pulmonary Disease in the Intensive Care Unit, Antibiotic Treatment of Severe Chronic Obstructive Pulmonary Disease Exacerbations*. Thieme Medical Publishers; 2020:830–841.
34. Pratt AJ, Purssell A, Zhang T, et al. Complexity in clinical diagnoses of acute exacerbation of chronic obstructive pulmonary disease. *BMC Pulmonary Medicine*. 2023;23(1):298. doi:10.1186/s12890-023-02587-1
35. Ammous O, Feki W, Lotfi T, et al. Inspiratory muscle training, with or without concomitant pulmonary rehabilitation, for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*. 2023;1:1.
36. Cousins JL. *Prescription of Acute Oxygen Therapy in Patients at Risk of Type Ii Respiratory Failure*. The University of Newcastle; 2023.
37. Pagliaro R, Aronne L, Fomez R, et al. High-flow nasal cannula system in respiratory failure associated with interstitial lung diseases, a systematic review and narrative synthesis. *J Clin Med*. 2024;13(10):2956. doi:10.3390/jcm13102956
38. Ferrer M, De Pascale G, Tanzarella ES, Antonelli M. *Severe Community-Acquired Pneumonia, Noninvasive Mechanical Ventilation, Intubation, and HFNT*. Thieme Medical Publishers, Inc.; 2024:169–186.
39. Carrillo-Aleml L, Agamez-Luengas AA, Guia M, et al. Effectiveness and safety of non-invasive ventilation in the management of cardiogenic shock. *Rev Portug Cardiol*. 2024;43(5):259–273. doi:10.1016/j.repc.2023.08.006
40. Baraldi F, Barrecheuren M, Papi A, Miravittles M. Managing exacerbations of COPD, how much progress have we made? *Eur Respir Soc*. 2024; 2024:283–296.
41. Longhini F, Vaschetto R, Navalesi P. Key messages. 2024:75.
42. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. *N Engl J Med*. 2024;390(24):2274–2283. doi:10.1056/NEJMoa2401304
43. Sun C-Y, Tesfaigzi Y, Lee G-Y, Chen Y-H, Weiss ST, KS-K M. Clinical effectiveness and safety of dupilumab in patients with chronic obstructive pulmonary disease, a 7-year population-based cohort study. *J Allergy Clin Immunol*. 2025;155(1):219–222.e1. doi:10.1016/j.jaci.2024.09.019
44. Yappalparvi A, Balaraman AK, Padmapriya G, et al. Safety and efficacy of ensifentrine in COPD, a systematic review and meta-analysis. *Respir Med*. 2025;236:107863. doi:10.1016/j.rmed.2024.107863
45. Nisa A, Kipper FC, Panigrahy D, Tiwari S, Kupz A, Subbian SJAJo P-CP. Different modalities of host cell death and their impact on Mycobacterium tuberculosis infection. *Am J Physiol Cell Physiol*. 2022;323(5):C1444–C1474.
46. Upton JE, Grunebaum E, Sussman G, Vadas PJB. Platelet activating factor (PAF), a mediator of inflammation. *BioFactors (Oxford, England)*. 2022;48(6):1189–1202. doi:10.1002/biof.1883
47. Shukla SD, Walters EH, Simpson JL, et al. Hypoxia-inducible factor and bacterial infections in chronic obstructive pulmonary disease. *Respirology (Carlton, Vic.)*. 2020;25(1):53–63. doi:10.1111/resp.13722
48. Brown MA. *The Epithelial Cell in Host-Pathogen Interactions in Airways Disease*. University of Oxford; 2022.
49. Beentjes D, Shears RK, French N, Neill DR, Kadioglu A, Medicine CC. Mechanistic insights into the impact of air pollution on pneumococcal pathogenesis and transmission. *Am J Respir Crit Care Med*. 2022;206(9):1070–1080. doi:10.1164/rccm.202112-2668TR
50. Rajendra KC. *Exploring Molecular Mechanisms Underlying the Role of Non-Typeable Haemophilus Influenzae in COPD*. University of Tasmania; 2020.
51. Kalininskiy A, Kittel J, Nacca NE, Misra RS, Croft DP, McGraw M. E-cigarette exposures, respiratory tract infections, and impaired innate immunity, a narrative review. *Pediat Med*. 2021;4. doi:10.21037/pm-20-97

52. Bagam P. *Role and Regulation of Autophagy Mechanism During Cigarette Smoke Exposure*. Southern University and Agricultural and Mechanical College; 2020.
53. Ferraro M, Di Vincenzo S, Lazzara V, et al. Formoterol exerts anti-cancer effects modulating oxidative stress and epithelial-mesenchymal transition processes in cigarette smoke extract exposed lung adenocarcinoma cells. *Int J Mol Sci*. 2023;24(22):16088. doi:10.3390/ijms242216088
54. Gusev SJJCIM. Analysis of the level of IgG to SARS-CoV-2 virus and molecular markers of activation of CD25, CD54 (ICAM-1) and CD95 lymphocytes in the patients who were not ill with COVID-19, recovered from COVID-19 and who had acute respiratory infections. The results of the correction of impaired immune homeostasis using the multitarget immunotherapy drug mercureid. *J Clin Immunol Microbiol*. 2022;3(3):1–17.
55. BJJjoms C. Secretome and tunneling nanotubes, a multilevel network for long range intercellular communication between endothelial cells and distant cells. *Int J Mol Sci*. 2021;22(15):7971. doi:10.3390/ijms22157971
56. Uhl LF, Gérard AJJo MS. Modes of communication between T cells and relevance for immune responses. *Int J Mol Sci*. 2020;21(8):2674. doi:10.3390/ijms21082674
57. Cribbs SK, Crothers K, Morris A. Pathogenesis of HIV-related lung disease, immunity, infection, and inflammation. *Physiol Rev*. 2020;100(2):603–632. doi:10.1152/physrev.00039.2018
58. Shukla SD, Shastri MD, Vanka SK, et al. Targeting intercellular adhesion molecule-1 (ICAM-1) to reduce rhinovirus-induced acute exacerbations in chronic respiratory diseases. *Inflammopharmacology*. 2022;30(3):725–735. doi:10.1007/s10787-022-00968-2
59. Osii RS, Otto TD, Garside P, Ndungu FM, Brewer JMFi I. The impact of malaria parasites on dendritic cell–T cell interaction. *Front Immunol*. 2020;11:1597. doi:10.3389/fimmu.2020.01597
60. Avadhanula V, Rodriguez CA, Ulett GC, Bakaletz LO, Adderson EEJL. Immunity. Nontypeable Haemophilus influenzae adheres to intercellular adhesion molecule 1 (ICAM-1) on respiratory epithelial cells and upregulates ICAM-1 expression. *Infect Immun*. 2006;74(2):830–838. doi:10.1128/IAI.74.2.830-838.2006
61. Michi AN, Yipp BG, Dufour A, Lopes F, Proud DJNC. PGC-1 α mediates a metabolic host defense response in human airway epithelium during rhinovirus infections. *Nature Commun*. 2021;12(1):3669. doi:10.1038/s41467-021-23925-z
62. Nesbitt H, Burke C, Haghgi M. Manipulation of the upper respiratory microbiota to reduce incidence and severity of upper respiratory viral infections, a literature review. *Front Microbiol*. 2021;12:713703. doi:10.3389/fmicb.2021.713703
63. Hyland I. *Synthesis and Functionalisation of Heterocyclic Molecules With Bioactive Properties*. University Of Tasmania; 2020.
64. Sharif NAJB. PAF-induced inflammatory and immuno-allergic ophthalmic diseases and their mitigation with PAF receptor antagonists, cell and nuclear effects. *Biofactors*. 2022;48(6):1226–1249.
65. Cima Cabal MD, Molina F, López-Sánchez JI, Pérez-Santín E, Del Mar García-Suárez M. Pneumolysin as a target for new therapies against pneumococcal infections, a systematic review. *PLoS One*. 2023;18(3):e0282970. doi:10.1371/journal.pone.0282970
66. Chen H-P, Xuan G, Zeng Q-LM. Progress in the treatment of chronic obstructive pulmonary diseases with traditional Chinese medicine. *Global J Med*. 2021;2(1):26–34.
67. Chen Y, Li M, Wen J, et al. Pharmacological activities of safflower yellow and its clinical applications. *Evid Based Compl Altern Med*. 2022;2022(1):2108557. doi:10.1155/2022/2108557
68. Coultas JA, Cafferkey J, Mallia P, Johnston EP. Experimental antiviral therapeutic studies for human rhinovirus infections. *J Exp Pharmacol*. 2021;2021:645–659.
69. Weichwald C, Zettl I, Ellinger I, et al. Antibody conjugates bispecific for pollen allergens and ICAM-1 with potential to prevent epithelial allergen transmigration and rhinovirus infection. *Int J Mol Sci*. 2023;24(3):2725. doi:10.3390/ijms24032725
70. Matthys A, Saelens XJAR. Promises and challenges of single-domain antibodies to control influenza. *Ant Res*. 2024;222:105807. doi:10.1016/j.antiviral.2024.105807
71. Parray HA, Shukla S, Perween R, et al. Inhalation monoclonal antibody therapy, a new way to treat and manage respiratory infections. *Applied Microbiol Biotechnol*. 2021;105(16–17):6315–6332. doi:10.1007/s00253-021-11488-4
72. Paul SS. *Characterization and Optimization of Interaction of Monoclonal Antibodies With Influenza a Hemagglutinin*. National University of Singapore (Singapore); 2018.
73. Oprita A, Baloi S-C, Staicu G-A, et al. Updated insights on EGFR signaling pathways in glioma. *Int J Mol Sci*. 2021;22(2):587. doi:10.3390/ijms22020587
74. Shi K, Wang G, Pei J, et al. Emerging strategies to overcome resistance to third-generation EGFR inhibitors. *J Hematol Oncol*. 2022;15(1):94. doi:10.1186/s13045-022-01311-6
75. Reuter JD, Myc A, Hayes MM, et al. Inhibition of viral adhesion and infection by sialic-acid-conjugated dendritic polymers. *Bioconjugate Chemistry*. 1999;10(2):271–278. doi:10.1021/bc980099n
76. Liu W, Liu Z, Zhang W, et al. Ulinastatin protects the lungs of COPD rats through the HMGB1/TLR4 signaling pathway. *Oncol Lett*. 2018;16(3):4057–4063. doi:10.3892/ol.2018.9123
77. Zeng X, Liu X, Bao H, Zhang Y, Tan EJC. Sulforaphane suppressed LPS and Pam3CSK4 mediated inflammation in COPD through MyD88-dependent toll-like receptors pathway. *Chest*. 2016;149(4):A351.
78. Zeng X, Liu X, Bao HJFOB. Sulforaphane suppresses lipopolysaccharide-and Pam3CysSerLys4-mediated inflammation in chronic obstructive pulmonary disease via toll-like receptors. *FEBS Open Bio*. 2021;11(5):1313–1321. doi:10.1002/2211-5463.13118
79. Ma J, Tian Y, Li J, et al. Effect of Bufei Yishen granules combined with Electroacupuncture in rats with chronic obstructive pulmonary disease via the regulation of TLR-4/NF- κ B signaling. *Evid Based Comp Altern Med*. 2019;2019(1):6708645. doi:10.1155/2019/6708645
80. Roy A, Srivastava M, Saqib U, et al. Potential therapeutic targets for inflammation in toll-like receptor 4 (TLR4)-mediated signaling pathways. *Int Immunopharmacol*. 2016;40:79–89. doi:10.1016/j.intimp.2016.08.026
81. Ramli I, Cheriet T, Posadino AM, et al. Potential therapeutic targets of resveratrol in the prevention and treatment of pulmonary fibrosis. *Front Biosci Landmark*. 2023;28(9). doi:10.31083/j.fbl2809198
82. Latsko KN, Jacob AT, Junod NA, et al. Role of differences in respiratory syncytial virus F and G glycoproteins on susceptibility to inactivation by antimicrobial peptides LL-37 and human beta-defensins. *Viral Immunol*. 2022;35(8):559–565. doi:10.1089/vim.2022.0063

83. Lehman HK, Segal B, Immunology C. The role of neutrophils in host defense and disease. *J Allergy Clin Immunol.* 2020;145(6):1535–1544. doi:10.1016/j.jaci.2020.02.038
84. Solanki SS, Singh P, Kashyap P, Sansi MS, SAJMp A. Promising role of defensins peptides as therapeutics to combat against viral infection. *Microbial Pathogenesis.* 2021;155:104930. doi:10.1016/j.micpath.2021.104930
85. Cahn A, Hamblin JN, Robertson J, et al. An inhaled PI3K δ inhibitor improves recovery in acutely exacerbating COPD patients, a randomized trial. *Int J Chronic Obst Pulm Dis.* 2021;16:1607–1619. doi:10.2147/COPD.S309129
86. Chan EWC, Kezuka M, Chan HT, Wong SK. The health-promoting properties of seaweeds, clinical evidence based on wakame and kombu. *J Nat Remed.* 2023;687–698. doi:10.18311/jnr/2023/30820
87. Negishi H, Mori M, Mori H, Yamori Y. Supplementation of elderly Japanese men and women with fucoidan from seaweed increases immune responses to seasonal influenza vaccination. *J Nutr.* 2013;143(11):1794–1798. doi:10.3945/jn.113.179036
88. Oliyaei N, Moosavi-Nasab M, Mazloomi SMJB. Therapeutic activity of fucoidan and carrageenan as marine algal polysaccharides against viruses. *3 Biotech.* 2022;12(7):154. doi:10.1007/s13205-022-03210-6
89. Cazzola M, Calzetta L, Rogliani P, Matera DD. The discovery of roflumilast for the treatment of chronic obstructive pulmonary disease. *Expert Opin Drug Discov.* 2016;11(7):733–744. doi:10.1080/17460441.2016.1184642
90. Tamaoki JJC. The effects of macrolides on inflammatory cells. *Chest.* 2004;125(2):41S–51S. doi:10.1378/chest.125.2_suppl.41s
91. Tajbakhsh A, Gheibihayat SM, Askari H, et al. Statin-regulated phagocytosis and efferocytosis in physiological and pathological conditions. *Pharmacol Therap.* 2022;238:108282. doi:10.1016/j.pharmthera.2022.108282
92. Anzueto A, Barjaktarevic IZ, Siler TM, et al. Ensifentrine, a novel phosphodiesterase 3 and 4 inhibitor for the treatment of chronic obstructive pulmonary disease, randomized, double-blind, placebo-controlled, multicenter Phase III trials (the ENHANCE trials). *Am J Respir Crit Care Med.* 2023;208(4):406–416. doi:10.1164/rccm.202306-0944OC
93. Dudek B, Rybka J, Bugla-Płoskońska G, et al. Biological functions of sialic acid as a component of bacterial endotoxin. *Front Microbiol.* 2022;13:1028796. doi:10.3389/fmicb.2022.1028796
94. Bel'skaya LV, Sarf EA, Solomatin DV, Kosenok VKJM. Features of the metabolic profile of saliva in lung cancer and COPD, the effect of smoking status. *Metabolites.* 2021;11(5):289. doi:10.3390/metabo11050289
95. Kirk NM, Liang Y, Ly HJP. Comparative pathology of animal models for influenza A virus infection. *Pathogens* 2023;13(1):35.
96. Benhaim M, Mangala Prasad V, Garcia N, Guttman M, KJSa L. Structural monitoring of a transient intermediate in the hemagglutinin fusion machinery on influenza virions. *Sci Adv.* 2020;6(18):eaaz8822. doi:10.1126/sciadv.aaz8822
97. Orr-Burks NL. *Host Genes as Antiviral Targets for Influenza Virus.* University of Georgia; 2021.
98. Sidletskaia K, Vitkina T, YJljocopd D. The role of toll-like receptors 2 and 4 in the pathogenesis of chronic obstructive pulmonary disease. *Int J Chronic Obst Pulm Dis.* 2020;15:1481–1493. doi:10.2147/COPD.S249131
99. Velasco WV, Khosravi N, Castro-Pando S, et al. Toll-like receptors 2, 4, and 9 modulate promoting effect of COPD-like airway inflammation on K-ras-driven lung cancer through activation of the MyD88/NF- κ B pathway in the airway epithelium. *Front Immunol.* 2023;14:1118721. doi:10.3389/fimmu.2023.1118721
100. Grassin-Delyle S, Abrial C, Salvator H, Brollo M, Naline E, Devillier P. The role of toll-like receptors in the production of cytokines by human lung macrophages. *J Innate Immun.* 2020;12(1):63–73. doi:10.1159/000494463
101. Kotlyarov SMS. Participation of ABCA1 transporter in pathogenesis of chronic obstructive pulmonary disease. *Int J Mol Sci.* 2021;22(7):3334. doi:10.3390/ijms22073334
102. Nucera F, Lo Bello F, Shen SS, et al. Role of atypical chemokines and chemokine receptors pathways in the pathogenesis of COPD. *Curr Med Chem.* 2021;28(13):2577–2653. doi:10.2174/0929867327999200819145327
103. Armitage MN, Spittle DA, Turner AMJB. A systematic review and meta-analysis of the prevalence and impact of pulmonary bacterial colonisation in stable state chronic obstructive pulmonary disease (COPD). *Biomedicines.* 2021;10(1):81. doi:10.3390/biomedicines10010081
104. Dicker AJ, Huang JT, Lonergan M, et al. The sputum microbiome, airway inflammation, and mortality in chronic obstructive pulmonary disease. *J Allergy Clin Immunol.* 2021;147(1):158–167. doi:10.1016/j.jaci.2020.02.040
105. Liu J, Ran Z, Wang F, Xin C, Xiong B, Song Z. Role of pulmonary microorganisms in the development of chronic obstructive pulmonary disease. *Crit Rev Microbiol.* 2021;47(1):1–12.
106. Zuo H, Cattani-Cavaliere I, Musheshe N, Nikolaev VO, Schmidt MJP. Phosphodiesterases as therapeutic targets for respiratory diseases. *Pharmacol Therap.* 2019;197:225–242. doi:10.1016/j.pharmthera.2019.02.002
107. Raker VK, Becker C, Steinbrink K. The cAMP pathway as therapeutic target in autoimmune and inflammatory diseases. *Front Immunol.* 2016;7:123. doi:10.3389/fimmu.2016.00123
108. Raju SV, Rasmussen L, Sloane PA, Tang LP, Libby EF, Rowe SMJRR. Roflumilast reverses CFTR-mediated ion transport dysfunction in cigarette smoke-exposed mice. *Respir Res.* 2017;18:1–8.
109. Mahler DA, Bhatt SP, Rheault T, et al. Effect of ensifentrine on dyspnea in patients with moderate-to-severe chronic obstructive pulmonary disease, pooled analysis of the ENHANCE trials. *Expert Rev Respir Med.* 2024;18(8):645–654. doi:10.1080/17476348.2024.2389960
110. Singh D, Lea S, Mathioudakis AGJD. Inhaled phosphodiesterase inhibitors for the treatment of chronic obstructive pulmonary disease. *Drugs.* 2021;81(16):1821–1830. doi:10.1007/s40265-021-01616-9
111. Pelaia C, Vatrella A, Gallelli L, et al. Role of p38 mitogen-activated protein kinase in asthma and COPD, pathogenic aspects and potential targeted therapies. *Drug Design, Development and Therapy.* 2021;15:1275–1284. doi:10.2147/DDDT.S300988
112. Dawson AR, Wilson GM, Freiburger EC, Mondal A, Coon JJ, Mehle A. Phosphorylation controls RNA binding and transcription by the influenza virus polymerase. *PLoS Pathogens.* 2020;16(9):e1008841. doi:10.1371/journal.ppat.1008841
113. Dey S, Mondal AJJo V. Unveiling the role of host kinases at different steps of influenza A virus life cycle. *J Virol.* 2024;98(1):e01192–23.
114. Strickland BA. *Mechanisms of Lactobacillus-Mediated Protection Against Respiratory Syncytial Virus Infection and Pathogenesis.* Vanderbilt University; 2022.
115. Hajjo R, Sabbah DA, Abusara OH, Kharmah R, Bardaweel SJV. Targeting human proteins for antiviral drug discovery and repurposing efforts, a focus on protein kinases. *Viruses.* 2023;15(2):568. doi:10.3390/v15020568
116. Griffiths C. Interactions between respiratory syncytial virus and cell surface nucleolin. 2020.

117. Blake ME, Kleinpeter AB, Jureka AS, et al. Structural investigations of interactions between the influenza a virus NS1 and host cellular proteins. *Viruses*. 2023;15(10):2063. doi:10.3390/v15102063
118. Zhang X, Zhang Y, Wei FJV. Research progress on the nonstructural protein 1 (NS1) of influenza a virus. *Virulence*. 2024;15(1):2359470. doi:10.1080/21505594.2024.2359470
119. He Y, Sun MM, Zhang GG, et al. Targeting PI3K/Akt signal transduction for cancer therapy. *Signal Transduct Target Ther*. 2021;6(1):425. doi:10.1038/s41392-021-00828-5
120. Zhang X, Ming Y, Fu X, et al. PI3K/AKT/p53 pathway inhibits infectious spleen and kidney necrosis virus infection by regulating autophagy and immune responses. *Fish Shellfish Immunol*. 2022;120:648–657. doi:10.1016/j.fsi.2021.12.046
121. Gopallawa I, Kuek LE, Adappa ND, Palmer JN, Lee RJ. Small-molecule Akt-activation in airway cells induces NO production and reduces IL-8 transcription through Nrf-2. *Respir Res*. 2021;22:1–17.
122. Moradi S, Jarrahi E, Ahmadi A, et al. PI3K signalling in chronic obstructive pulmonary disease and opportunities for therapy. *J Pathol*. 2021;254(5):505–518. doi:10.1002/path.5696
123. Fagone E, Fruciano M, Gili E, Sambataro G, Vancheri C. Developing PI3K inhibitors for respiratory diseases. In, *PI3K and AKT Isoforms in Immunity, Mechanisms and Therapeutic Opportunities*. Springer; 2022:437–466.
124. Cai B, Liu M, Li J, Xu D, Li JF, Toxicology C. Cigarette smoke extract amplifies NADPH oxidase-dependent ROS production to inactivate PTEN by oxidation in BEAS-2B cells. *Food Chem Toxicol*. 2021;150:112050. doi:10.1016/j.fct.2021.112050
125. Liu J, Liang Q, Wang T, et al. IFN- τ mediated miR-26a targeting PTEN to activate PI3K/AKT signalling to alleviate the inflammatory damage of bEECs. *Sci Rep*. 2022;12(1):9410. doi:10.1038/s41598-022-12681-9
126. Chen-Yu Hsu A, Starkey MR, Hanish I, et al. Targeting PI3K-p110 α suppresses influenza virus infection in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;191(9):1012–1023. doi:10.1164/rccm.201501-0188OC
127. Lanahan SM, Wymann MP, Lucas CLJNRI. The role of PI3K γ in the immune system, new insights and translational implications. *Nat Rev Immunol*. 2022;22(11):687–700. doi:10.1038/s41577-022-00701-8
128. Conese M, Di Gioia SJP. Pathophysiology of lung disease and wound repair in cystic fibrosis. *Pathophysiology*. 2021;28(1):155–188. doi:10.3390/pathophysiology28010011
129. Jakiela B, Rebane A, Soja J, et al. Remodeling of bronchial epithelium caused by asthmatic inflammation affects its response to rhinovirus infection. *Sci Rep*. 2021;11(1):12821. doi:10.1038/s41598-021-92252-6
130. Tan CL, Chan Y, Candasamy M, et al. Unravelling the molecular mechanisms underlying chronic respiratory diseases for the development of novel therapeutics via in vitro experimental models. *Eur J Pharmacol*. 2022;919:174821. doi:10.1016/j.ejphar.2022.174821
131. Janssen-Heininger Y, Reynaert NL, van der Vliet A, Anathy V. Endoplasmic reticulum stress and glutathione therapeutics in chronic lung diseases. *Redox Biology*. 2020;33:101516. doi:10.1016/j.redox.2020.101516
132. Alshammari JO. *IL-36 and IL-37 Cytokines, Mediators or Potential Modulators of Airway Infection and Inflammation*. The University of Liverpool (United Kingdom); 2022.
133. Morris DE. *The Epidemiology of Moraxella Catarrhalis*. University of Southampton; 2022.
134. Velkova SA. *Moraxella Catarrhalis and Rhinovirus Infection and Co-Infection of Healthy and Chronic Obstructive Pulmonary Disease Ciliated Respiratory Epithelium*. UCL (University College London); 2020.
135. Zhao J, Lang M. New insight into protein glycosylation in the development of Alzheimer's disease. *Cell Death Discovery*. 2023;9(1):314. doi:10.1038/s41420-023-01617-5
136. Gu J, Isaji TJGJ. Specific sialylation of N-glycans and its novel regulatory mechanism. 2024
137. Irons EE, Gc S, Lau JTJI. Sialic acid in the regulation of blood cell production, differentiation and turnover. *Immunology*. 2024;172(4):517–532. doi:10.1111/imm.13780
138. Singh P, Joon A, Kumari M, et al. Role of a disease-associated ST3Gal-4 in non-small cell lung cancer. *Cell Biochemistry and Biophysics*. 2022;80(4):781–793. doi:10.1007/s12013-022-01091-3
139. Xie X, Kong S, Cao WJFi I. Targeting protein glycosylation to regulate inflammation in the respiratory tract, novel diagnostic and therapeutic candidates for chronic respiratory diseases. *Front Immunol*. 2023;14:1168023. doi:10.3389/fimmu.2023.1168023
140. Krick S, Helton ES, Easter M, et al. ST6GAL1 and alpha 2-6 sialylation regulates IL-6 expression and secretion in chronic obstructive pulmonary disease. *Front Immunol*. 2021;12:693149. doi:10.3389/fimmu.2021.693149
141. El Kebir D, Filep J. Modulation of neutrophil apoptosis and the resolution of inflammation through β 2 integrins. *Front Immunol*. 2013;4:60. doi:10.3389/fimmu.2013.00060
142. Goyal M, Singh M, Ray P, Srinivasan R, Chakraborti AJPD. Cellular interaction of nontypeable Haemophilus influenzae triggers cytotoxicity of infected type II alveolar cells via apoptosis. *Pathog Dis*. 2015;73(2):1–12. doi:10.1111/2049-632X.12215
143. Rahman F, Chebbo M, Courtin N, Fotso Fotso A, Alessi MC, Riteau B. The Annexin A1 Receptor FPR2 regulates the endosomal export of influenza virus. *Int J Mol Sci*. 2018;19(5):1400. doi:10.3390/ijms19051400
144. Kamel AA, Hashem MK, AbdulKareem ES, et al. Significant interrelations among serum Annexin A1, Soluble Receptor for Advanced Glycation End Products (sRAGE) and rs2070600 in chronic obstructive pulmonary disease. *Biology*. 2022;11(12):1707. doi:10.3390/biology11121707
145. Lai T, Li Y, Mai Z, et al. Annexin A1 is elevated in patients with COPD and affects lung fibroblast function. *Int J Chron Obstruct Pulmon Dis*. 2018;13:473–486. doi:10.2147/COPD.S149766
146. Tavares LP, Galvão I, Ferrero MRJCP. Novel immunomodulatory therapies for respiratory pathologies. *Comprehens Pharmacol* 2022; 2022, 554.
147. Schlösser D. Macrophage phenotypes and repair function in lung fibrosis. 2024.
148. Grigoryeva LS, Cianciotto NP. Human macrophages utilize a wide range of pathogen recognition receptors to recognize Legionella pneumophila, including toll-like receptor 4 engaging Legionella lipopolysaccharide and the toll-like receptor 3 nucleic-acid sensor. *PLoS Pathog*. 2021;17(7):e1009781. doi:10.1371/journal.ppat.1009781
149. Ogger PP, Byrne AJ. Macrophage metabolic reprogramming during chronic lung disease. *Mucosal Immunol*. 2021;14(2):282–295. doi:10.1038/s41385-020-00356-5
150. Strizova Z, Benesova I, Bartolini R, et al. M1/M2 macrophages and their overlaps - myth or reality? *Clin Sci*. 2023;137(15):1067–1093. doi:10.1042/CS20220531

151. Chen S, Saeed A, Liu Q, et al. Macrophages in immunoregulation and therapeutics. *Signal Transduct Target Ther.* 2023;8(1):207. doi:10.1038/s41392-023-01452-1
152. Canton M, Sanchez-Rodriguez R, Spera I, et al. Reactive oxygen species in macrophages, sources and targets. *Front Immunol.* 2021;12:734229. doi:10.3389/fimmu.2021.734229
153. Wang X, Murugesan P, Zhang P, et al. NADPH oxidase isoforms in COPD patients and acute cigarette smoke-exposed mice, induction of oxidative stress and lung inflammation. *Antioxidants.* 2022;11(8):1539. doi:10.3390/antiox11081539
154. Akata K, Yamasaki K, Leitao Filho FS, et al. Abundance of Non-polarized lung macrophages with poor phagocytic function in Chronic Obstructive Pulmonary Disease (COPD). *Biomedicines.* 2020;8(10):398. doi:10.3390/biomedicines8100398
155. Zhou X, Liu X, Huang L. Macrophage-mediated tumor cell phagocytosis, opportunity for nanomedicine intervention. *Adv Funct Mater.* 2021;31(5). doi:10.1002/adfm.202006220
156. Kotlyarov S. Involvement of the innate immune system in the pathogenesis of chronic obstructive pulmonary disease. *Int J mol Sci.* 2022;23(2):985. doi:10.3390/ijms23020985
157. Lea S, Beech A, Baker J, et al. Differential responses of COPD macrophages to respiratory bacterial pathogens. *ERJ Open Res.* 2022;8(3):00044–2022. doi:10.1183/23120541.00044-2022
158. Yadav S, Dwivedi A, Tripathi A. Biology of macrophage fate decision, implication in inflammatory disorders. *Cell Biol Int.* 2022;46(10):1539–1556. doi:10.1002/cbin.11854
159. Hartl D, Tirouvanziam R, Laval J, et al. Innate immunity of the lung, from basic mechanisms to translational medicine. *J Innate Immun.* 2018;10(5–6):487–501. doi:10.1159/000487057
160. Lugg ST, Scott A, Parekh D, Naidu B, Thickett DR. Cigarette smoke exposure and alveolar macrophages, mechanisms for lung disease. *Thorax.* 2022;77(1):94–101. doi:10.1136/thoraxjnl-2020-216296
161. Huang X, He D, Pan Z, Luo G, Deng JJMTB. Reactive-oxygen-species-scavenging nanomaterials for resolving inflammation. *Mater Today Bio.* 2021;11:100124. doi:10.1016/j.mtbio.2021.100124
162. Russo P, Milani F, De Iure A, et al. Effect of cigarette smoking on clinical and molecular endpoints in COPD patients. *Int J Mol Sci.* 2024;25(11):5834.
163. Garcia-Ryde M, van der Burg NMD, Berlin F. Stress response in chronic obstructive pulmonary disease-effect of cigarette smoke extract and hypoxia on structural lung cells. *Int J Mol Sci.* 2024;25(12). doi:10.3390/ijms25126600
164. Bezerra FS, Lanzetti M, Nesi RT, et al. Oxidative stress and inflammation in acute and chronic lung injuries. *Antioxidants.* 2023;12(3). doi:10.3390/antiox12030548
165. Moghadam ZM, Henneke P, Kolter J. biology d. From flies to men, ROS and the NADPH oxidase in phagocytes. *Front Cell Dev Biol.* 2021;9:628991. doi:10.3389/fcell.2021.628991
166. Nucera F, Mumby S, Paudel KR, et al. Role of oxidative stress in the pathogenesis of COPD. *Minerva Med.* 2022;113(3):370–404. doi:10.23736/S0026-4806.22.07972-1
167. Herb M, Schramm M. Functions of ROS in macrophages and antimicrobial immunity. *Antioxidants.* 2021;10(2). doi:10.3390/antiox10020313
168. To EE, O’Leary JJ, O’Neill LAJ, et al. Spatial properties of reactive oxygen species govern pathogen-specific immune system responses. *Antioxid Redox Signal.* 2020;32(13):982–992. doi:10.1089/ars.2020.8027
169. Barnes PJ. Oxidative stress in chronic obstructive pulmonary disease. *Antioxidants.* 2022;11(5):965. doi:10.3390/antiox11050965
170. Erlich JR, To EE, Liong S, et al. Targeting evolutionary conserved oxidative stress and immunometabolic pathways for the treatment of respiratory infectious diseases. *Antioxidants Redox Sig.* 2020;32(13):993–1013. doi:10.1089/ars.2020.8028
171. Chan SM, Bernardo I, Mastronardo C, et al. Apocynin prevents cigarette smoking-induced loss of skeletal muscle mass and function in mice by preserving proteostatic signalling. *Br J Pharmacol.* 2021;178(15):3049–3066. doi:10.1111/bph.15482
172. Schiffers C, Reynaert NL, Wouters EF, van der Vliet AJA. Redox dysregulation in aging and COPD, role of NOX enzymes and implications for antioxidant strategies. *Antioxidants.* 2021;10(11):1799. doi:10.3390/antiox10111799
173. Bayarri MA, Milara J, Estormut C, Cortijo J. Nitric oxide system and bronchial epithelium, more than a barrier. *Front Physiol.* 2021;12:687381. doi:10.3389/fphys.2021.687381
174. Schanne G, Demignot S, Policar C, Delsuc NJCCR. Cellular evaluation of superoxide dismutase mimics as catalytic drugs, challenges and opportunities. *Coordination Chem Rev.* 2024;514:215906.
175. Chen D, Zheng R, Su J, et al. Inhibition of H1N1 influenza virus-induced apoptosis by Ebselen through ROS-mediated ATM/ATR signaling pathways. *Biological Trace Element Res.* 2023;201(6):2811–2822. doi:10.1007/s12011-022-03369-2
176. Ferrer JLM, Garcia RLJC. Antioxidant systems, lncRNAs, and tunneling nanotubes in cell death rescue from cigarette smoke exposure. *Cells.* 2022;11(15):2277. doi:10.3390/cells11152277
177. Zhang F, Xiang Y, Ma Q, Guo E, Zeng O. A deep insight into ferroptosis in lung disease, facts and perspectives. *Front Oncolo.* 2024;14:1354859. doi:10.3389/fonc.2024.1354859
178. Khan MI, Khan M, Mannino D. The new epidemiology of COPD. COPD in the 21st Century (ERS Monograph). *Eur Respir Soc* 2024. 63–80.
179. Ho T, Nichols M, Nair G, et al. Iron in airway macrophages and infective exacerbations of chronic obstructive pulmonary disease. *Respir Res.* 2022;23(1):8. doi:10.1186/s12931-022-01929-7
180. Zhou J, Du JY, Xu R, Wu XJ, Zhang GYJTKJo MS. Reduced miR-513a-5p expression in COPD may regulate airway mucous cell hyperplasia through TFR1-dependent signaling. *Kaohsiung J Med Sci.* 2024;40(2):139–149. doi:10.1002/kjm2.12777

International Journal of Chronic Obstructive Pulmonary Disease

Dovepress

Taylor & Francis Group

Publish your work in this journal

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management protocols. This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal>