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REVIEW

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

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**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 β2-agonists (LABA)

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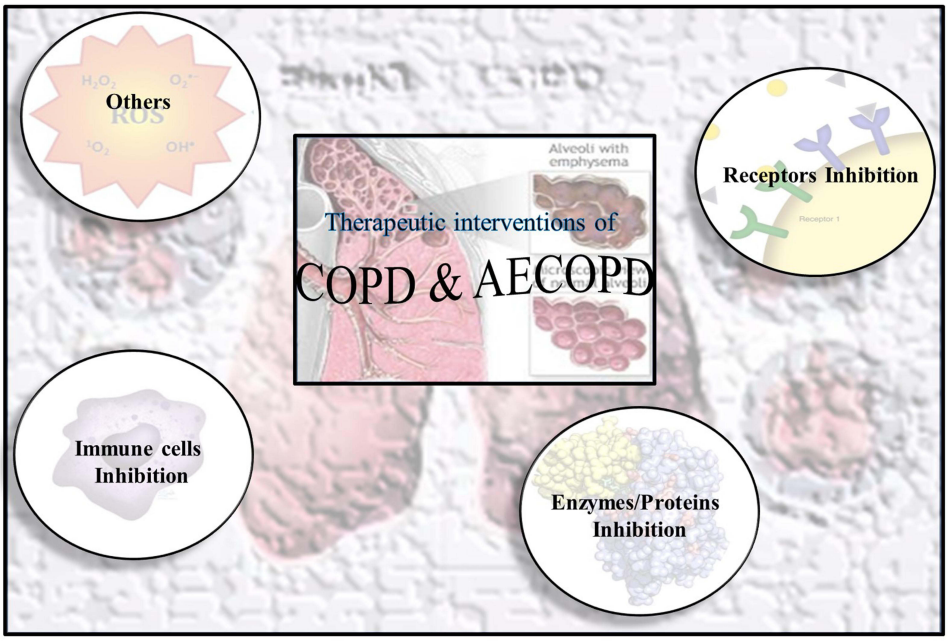
**Graphical Abstract**




and long-acting anti-muscarinic agonists (LAMA), alongside corticosteroids (inhaled or oral) antibiotics[6] 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-esinophilic 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 | *Influenza, Picornavirus, Respiratory Syncytial Virus, Coronaviruses, Parainfluenza, Adenovirus, Human Metapneumovirus* | 34% | Deterioration of lung function, prolonged hospital stay, and more severe clinical course and worse hypoxaemia | [14–19] |
| Bacterial infection | *Pseudomonas aeruginosa, Klebsiella pneumoniae and Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae* | 26% to 81% | Co-infection with viruses, 9% to 19% prevalence, leading to worse clinical outcomes | [20–22] |
| Outdoor pollutants | Sulphur dioxide (SO2), Nitrogen dioxide (NO2), Ozone (O3), carbon monoxide (CO), Small-diameter particulate matter (PM)2.5, PM1022 and coarse PM (2.5–10-μm aerodynamic diameter) | 4% to 38% | Significant decline in mortality with reduced SO2 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] |


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**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 PaO2 at 7.3–10 kPa (SaO2 85–92%).The Free O2 device can improve target SaO2 maintenance and reduce hospital stay length. | | [36] |
| **High Flow Nasal Cannula (HFNC)** | Used during severe hypoxemic acute respiratory failure (ARF). | | | HFNC delivers high FiO2 with positive pressure and nasopharyngeal dead space washout.<br>Improves oxygenation, breathing pattern, and reduces work of breathing.<br>Safe for stable hypercapnic patients.<br>Recent studies show similar intubation and mortality rates compared to conventional oxygen therapy and NIMV.<br>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 ≤7.35).<br>Minimizes risks, complications, duration of hospital stay, and intubation necessity.<br>Cost-effective strategy.<br>New helmet interface and helium/oxygen mixture may improve tolerance and gas exchange.<br>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] |
| **Ensifentrine** | 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] |

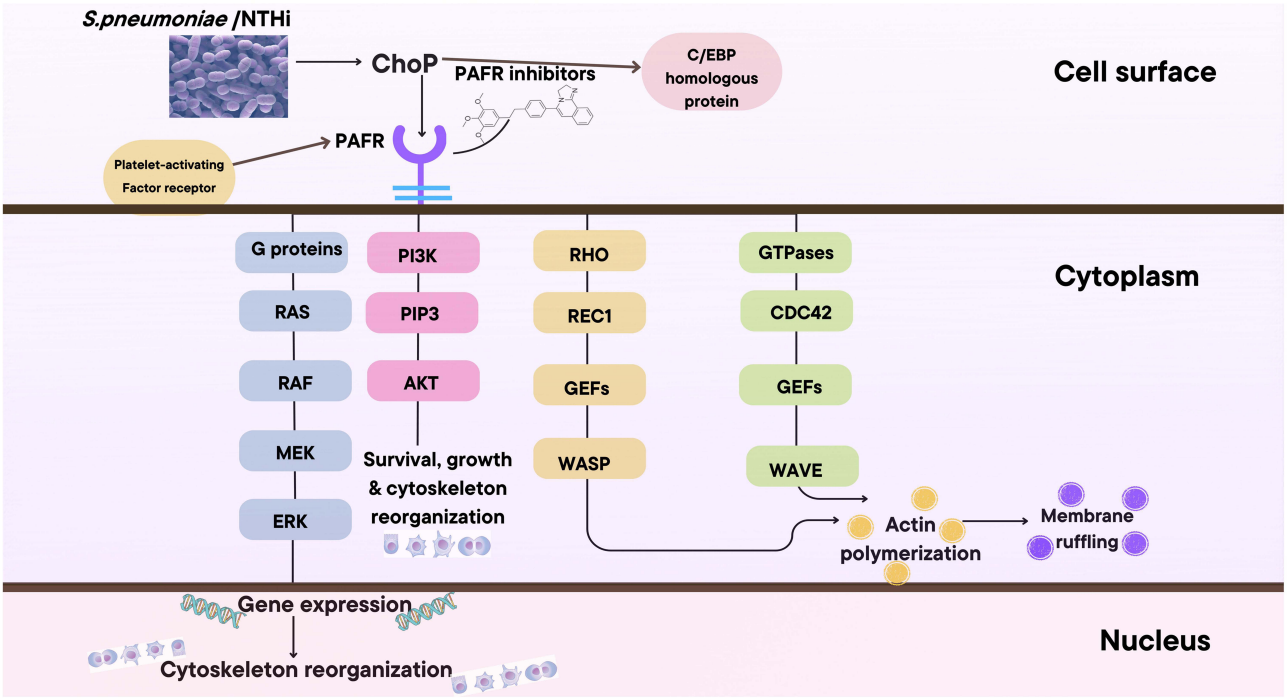


**Figure 1** Platelet activating factor receptor (PAFr) inhibition as therapeutic approach for COPD.
**Abbreviations**, ANTHi, nontypeable *Haemophilus Influenza*; ChoP, phosphorylcholine; Ras, rat sarcoma, Raf, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase; ERK, extracellular 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 1; 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 1 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 | PI3Kδ 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 expression[60] 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-1β, 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 al[94] 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 SAα2,6Gal and SAα2,3Gal 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

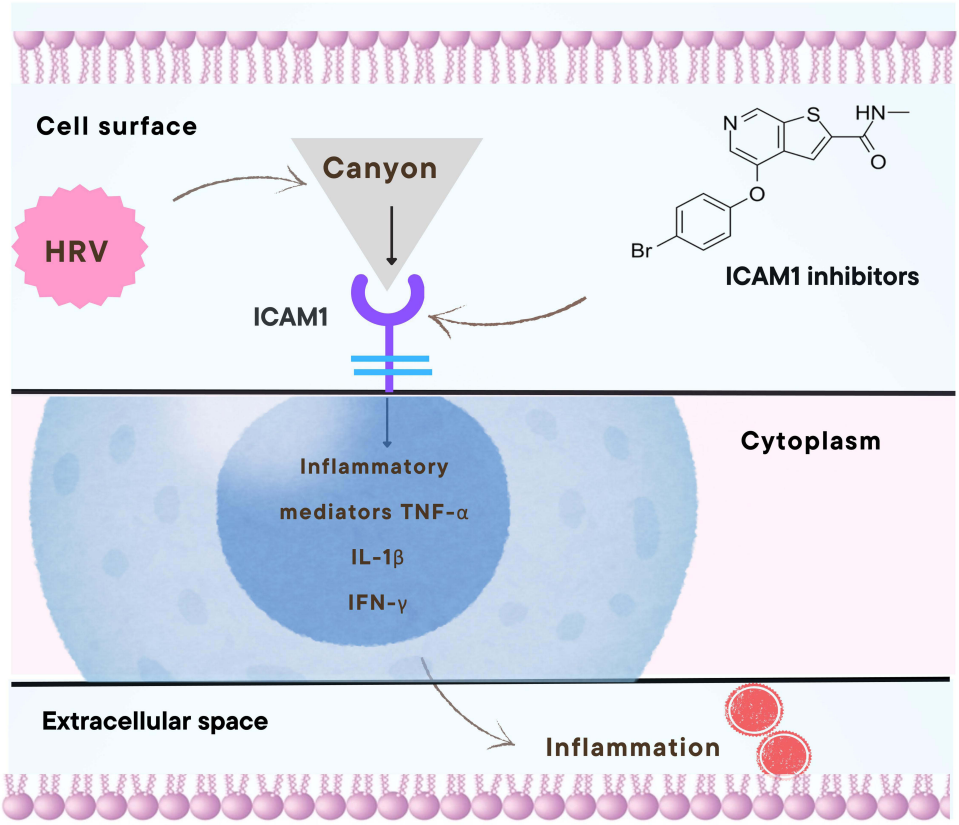


**Figure 2** Intracellular adhesion molecule-1 (ICAM-1) inhibition as therapeutic approach for COPD.
**Abbreviations**, HRV, human rhinovirus; TNF-α, tumor necrosis factor-α; IL-1β, Interleukin 1β; IFN-γ, Interferon γ.

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-kB, and IRF3[97] (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 damage[99] (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-κB (NF-κB), 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.

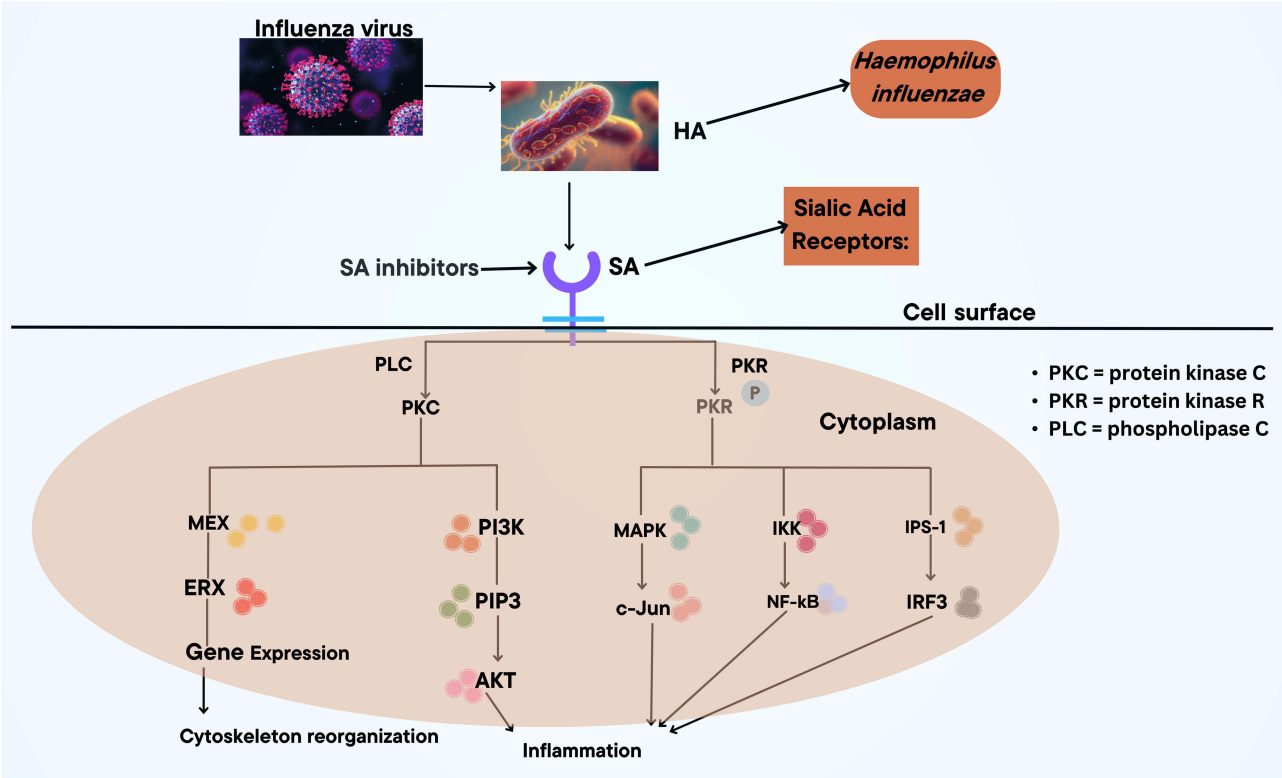


**Figure 3** Sialic acid (SA) inhibition as therapeutic approach for COPD.
**Abbreviations**: HA, Heamagglutinin; PLC, phospholipase C; PKC, Protein kinase C; ERK, extracellular signal regulated kinase; PKR, Protein kinase R; PKR-P, Protein kinase R-phosphorylated; MAPK, Mitogen activated protein kinase; IKK, IκB kinase; IPS-1, Interferon-β Promoter Stimulator 1; c-Jun, A component of the activator protein 1; Nf-kB, Nuclear factor kappa B; IRF3, Interferon regulatory factor 3.


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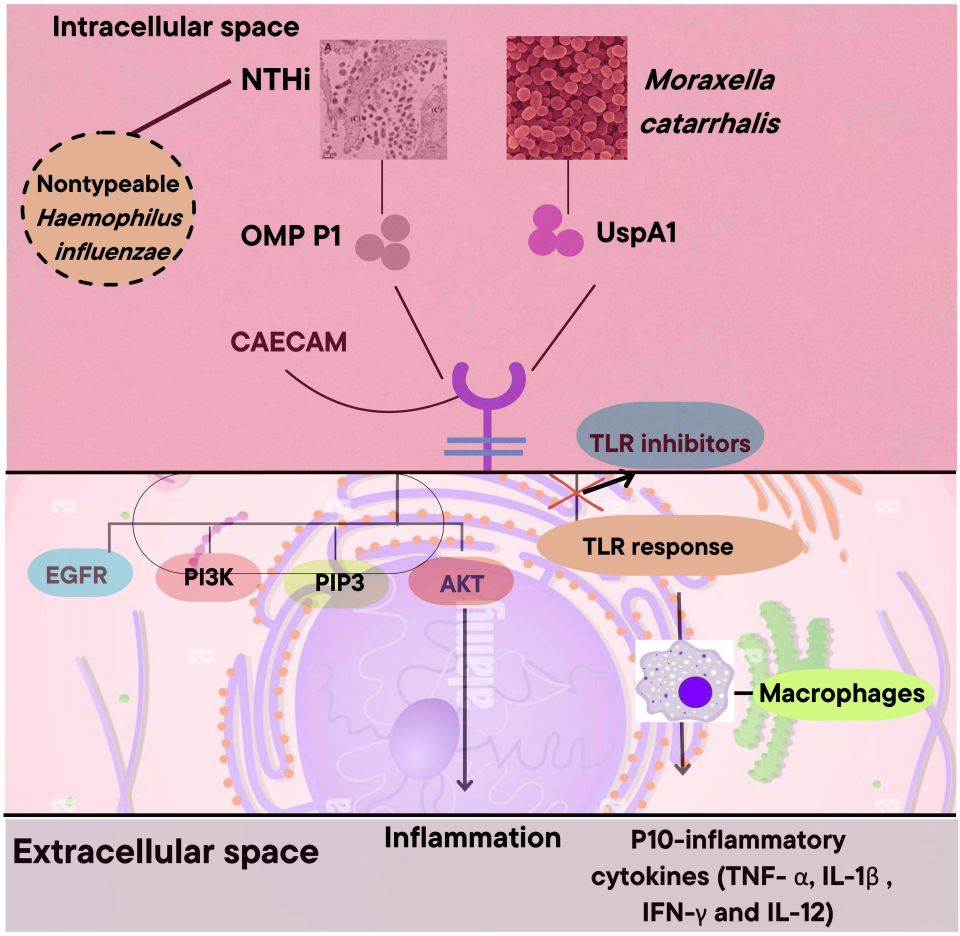


**Figure 4** TLR inhibition as therapeutic approach for COPD.
**Abbreviations**: NTHi, nontypeable *Haemophilus Influenza*; OMP P1, Outer membrane protein P1; UspA1, Ubiquitous surface protein A1; EGFR, Epidermal growth factor receptor; TLR, Toll-like receptor; IL-1β, Interleukin 1β; IFN-γ, Interferon 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

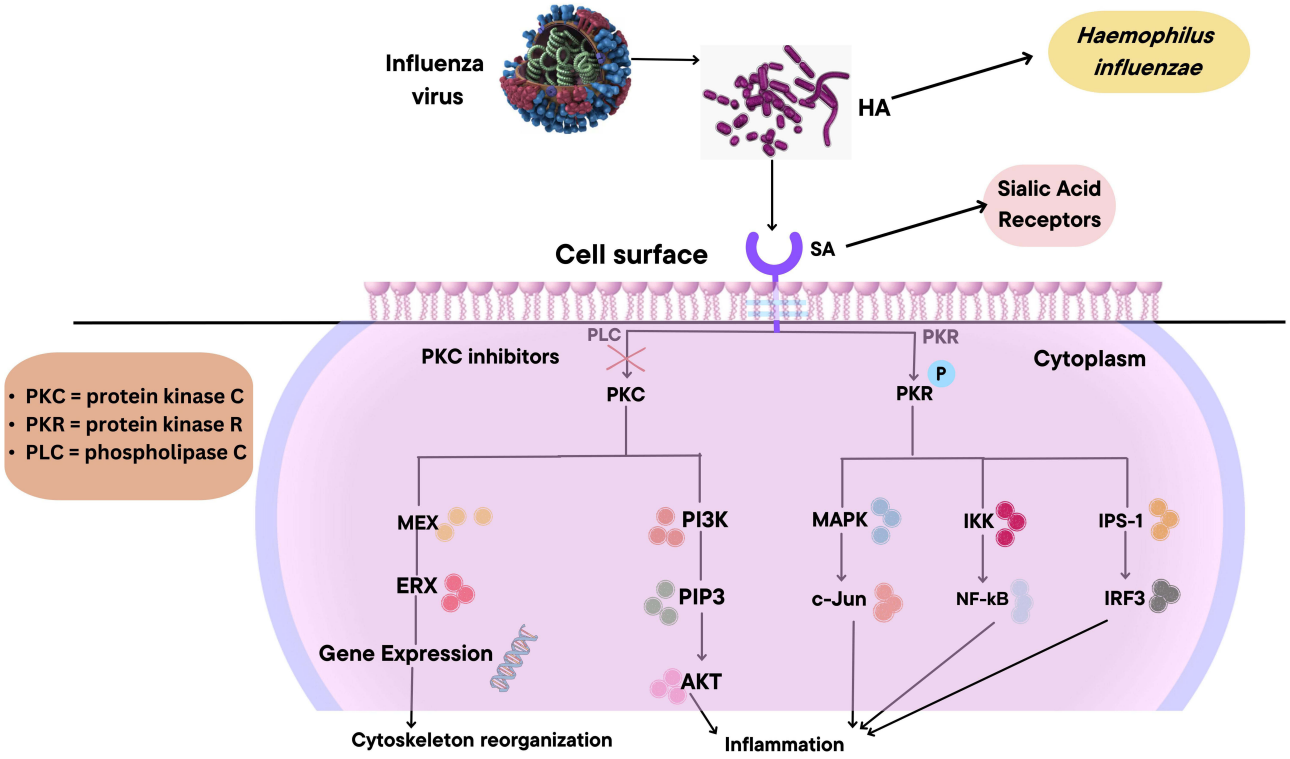


**Figure 5** Protein kinase C Inhibition as therapeutic approach for COPD.

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, PKCbII 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 cells[116] (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-p110α isoform is notably overexpressed in primary bronchial epithelial cells (pBECs) from COPD patients. Reducing p110α expression prior to infection has been shown to decrease viral effects and enhance the antiviral response mediated by IFN-β,


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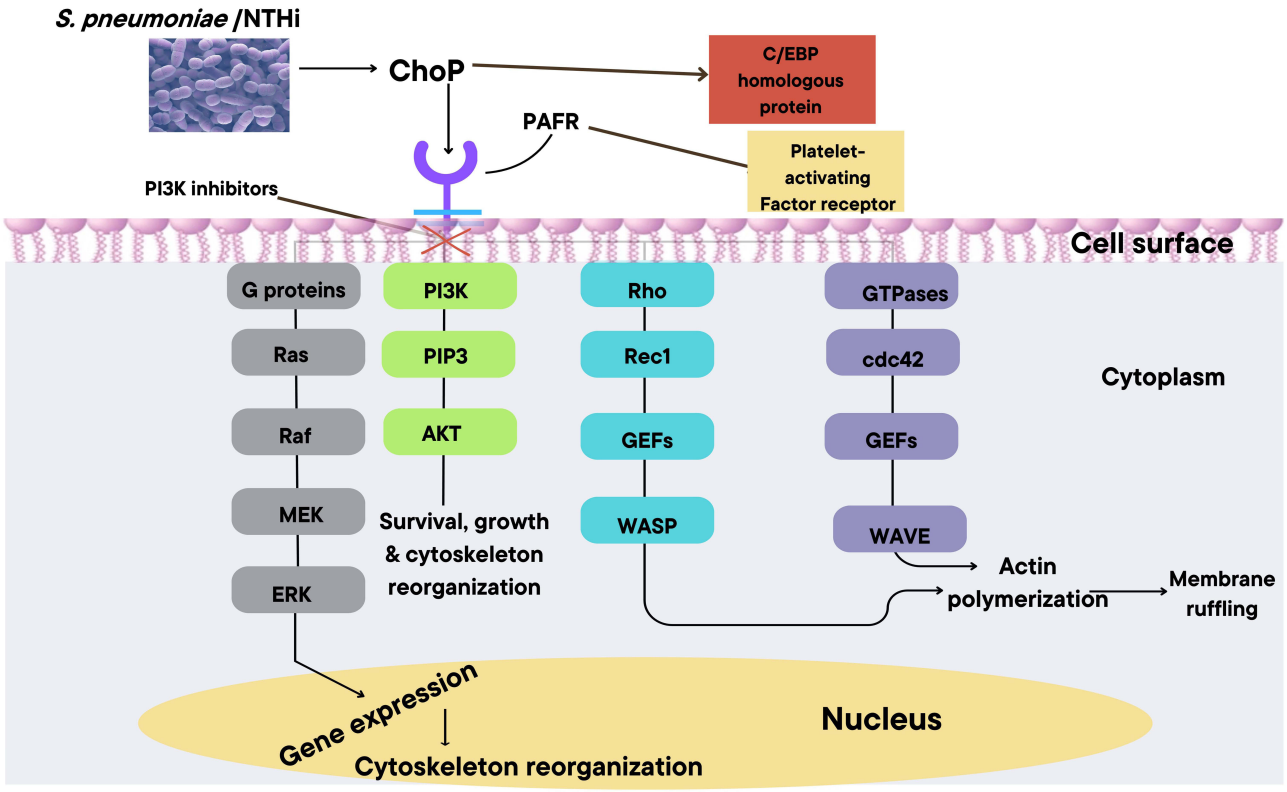


**Figure 6** Phosphoinositide 3-kinase inhibition as therapeutic approach for COPD.

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, PI3Ky, 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 1 (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 α2-6 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 al[140] 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 α2-6 sialylation, and increased IL-6 levels in HBECs. This relationship between ST6GAL1 and IL-6 suggests that decreased ST6GAL1 levels, with subsequent α2-6 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 α2-6 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 α2-6 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 highlight 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-1β, 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 macrophages 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]

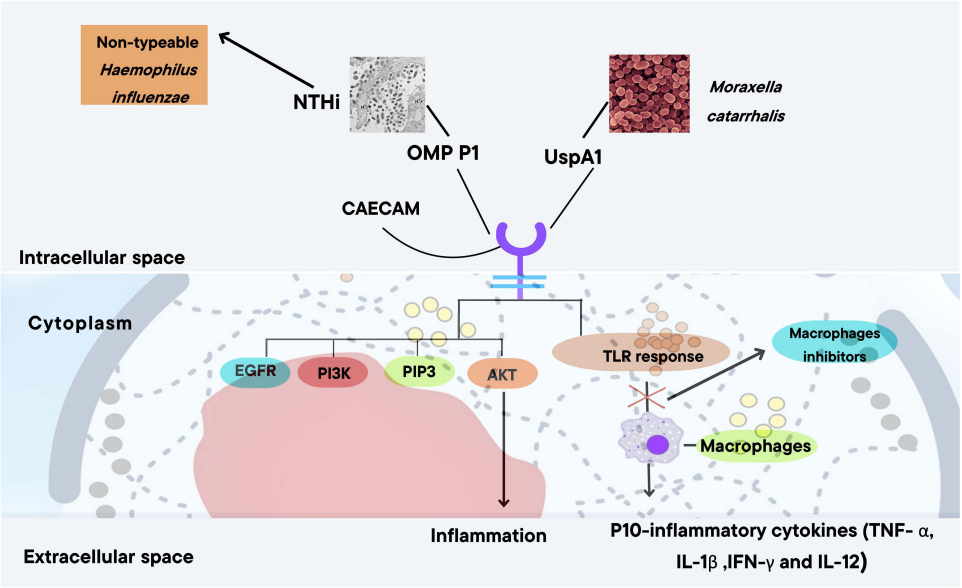


**Figure 7** Macrophage Inhibition as therapeutic approach for COPD.

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 al[179] 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.

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## Disclosure

The authors declare no conflicts of interest in this work.

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