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Chemokines and inflammation in COPD: implications for targeted therapy

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ABSTRACT

A severe global health issue, chronic obstructive pulmonary disease (COPD) is characterised by recurrent respiratory symptoms and restricted breathing because of long-term lung inflammation. A class of minuscule cytokines known as chemokines is essential for immune cell recruitment and activation, which sustains the inflammatory response in COPD. This study thoroughly examines the origins, modes of action and effects of chemokines on developing COPD-related inflammation. We detail the involvement of key chemokines, such as CXCL9, CXCL10, and CXCL11, in COPD pathophysiology. These chemokines are integral in attracting neutrophils, macrophages, and T lymphocytes to the lungs, leading to chronic inflammation, airway remodelling, and emphysema. Increased levels of these chemokines correlate with increased disease severity and frequency of exacerbations. The review additionally examines the possibility of using chemokine pathway targeting as a treatment approach. Current COPD treatments primarily address symptoms without adequately controlling underlying inflammation. By inhibiting chemokine signalling, it may be possible to reduce inflammation, slow disease progression, and improve patient outcomes. We discuss various therapeutic approaches, including developing chemokine receptor inhibitors, biologics such as monoclonal antibodies, drug repurposing, and combination therapies with existing treatments.

Furthermore, we review ongoing and completed clinical trials investigating chemokine-targeted therapies in COPD, highlighting their efficacy and safety. This review also emphasises the need for further research to optimise these therapies and identify biomarkers for monitoring treatment response. In conclusion, chemokines are pivotal in the inflammatory processes of COPD. Targeting chemokine pathways presents a promising avenue for developing more effective treatments, which could significantly enhance patient care and disease management.

Introduction

A prevalent and chronic respiratory condition known as chronic obstructive pulmonary disease (COPD) is marked by continuous airflow restriction and long-term respiratory symptoms such as coughing up phlegm, producing mucus, and dyspnea. It mainly results from prolonged exposure

to toxic gases and particles, mostly from tobacco smoking, but also from occupational and environmental contaminants. COPD encompasses chronic bronchitis and emphysema, conditions that often coexist and lead to significant lung damage and impaired pulmonary function [1]. The impact of COPD extends beyond the respiratory system, affecting the overall quality of life and daily functioning of individuals. It is a primary global source of morbidity and mortality, placing a significant strain on healthcare systems because of the need for long-term care, frequent hospital stays, and related comorbidities such as metabolic and cardiovascular illnesses. The progressive nature of COPD results in a gradual decline in lung function, increased risk of acute exacerbations, and a higher mortality rate, contributing to a significant socioeconomic burden [2]

Chronic inflammation is a significant contributing element to the pathophysiology of chronic obstructive pulmonary disease (COPD). Chronic exposure to gases and particles in the air, particularly cigarette smoke, inflames the airways and lung parenchyma. This reaction is characterised by the activation and recruitment of several immune cells, including neutrophils, T lymphocytes, and macrophages, which release inflammatory mediators, including chemokines and cytokines [2]. These mediators cause continuous tissue remodelling and injury by sustaining the inflammatory cycle. Airflow restriction and poor gas exchange are caused by structural alterations to the lung tissue and airways brought on by the chronic inflammatory process associated with COPD. These changes include fibrosis, mucus hypersecretion, and the breakdown of alveolar walls. Prolonged inflammation not only causes damage to lung tissue but also seeps into the bloodstream, exacerbating coexisting illnesses, including muscular atrophy and cardiovascular disease [3]. Comprehending the pivotal function of inflammation in the pathophysiology of COPD is imperative to discern therapeutic targets capable of modulating the inflammatory response, diminishing tissue damage, and ameliorating patient outcomes.

Chemokines are micro-signalling proteins that are essential for controlling inflammation and the immune system. In reaction to inflammatory stimuli like infection or tissue damage, leukocytes, endothelial cells, and fibroblasts are among the cell types that release them. By attaching to particular receptors on immune cell surfaces and guiding them toward areas of infection or inflammation, chemokines control the movement and activation of immune cells. Leukocyte recruitment to the site of damage is crucial for the removal of pathogens and the start of tissue repair processes [4]. Besides their function in immune cell trafficking, chemokines also influence leukocyte activation, adhesion, and survival in the inflammatory response. They facilitate the extravasation of immune cells from the bloodstream into the tissue by controlling the contacts between the immune cells and the endothelium. Additionally, pro-inflammatory cytokines and other mediators can be released in response to chemokines, intensifying the inflammatory response and encouraging tissue damage [5].

This study aims to clarify how chemokines contribute to inflammation associated with COPD and to discuss the possibility that targeted chemokine medicinal products may help COPD patients achieve better treatment outcomes. This review also examines the processes by which chemokines contribute to inflammation in COPD by a thorough analysis of recent research findings, including their role in immune cell recruitment, tissue damage, and disease progression [6]. The evaluation also assesses the safety and effectiveness of targeted chemokine treatments in preclinical and clinical settings, providing information about their potential as cutting-edge COPD treatment modalities.

Role of chemokines in COPD inflammation

Key chemokines involved in COPD (e.g., CXCL9, CXCL10, CXCL11)

A group of miniature signalling proteins known as chemokines is involved in directing immune cells to areas of inflammation or injury, where they take part in host defence, tissue repair, and immune surveillance. Chemokines regulate the migration, activation, and adherence of target cells by binding to specific receptors on their surface. Numerous chemokines are significant mediators of inflammation in the lung parenchyma and airways in the context of Chronic Obstructive Pulmonary Disease (COPD). It has been determined

that CXCL9, CXCL10, and CXCL11 play a significant role in the pathogenesis of COPD [7]. These chemokines, which belong to the CXC chemokine subfamily, are connected by the CXCR3 receptor, which is expressed on a range of immune cells, including natural killer cells, T lymphocytes, and dendritic cells.

When triggered with interferon-gamma (IFN-γ), activated macrophages and dendritic cells are the primary producers of CXCL9, also known as monokine produced by interferon-gamma (MIG). CXCL9 functions as a chemoattractant for T lymphocytes, namely T helper 1 (Th1) cells, which express CXCR3 at high levels. Patients with COPD have elevated CXCL9 levels in their lung tissue and airways, and these levels are linked to the severity of the condition and airflow restriction [8]. Th1 cells are drawn to the lungs by CXCL9, where they produce pro-inflammatory cytokines and cause tissue damage and persistent inflammation. Moreover, CXCL9 signalling has been implicated in airway remodelling by promoting fibroblast proliferation and extracellular matrix deposition, which exacerbates lung function decline in COPD. Studies have shown that CXCL9 expression in bronchial epithelial cells is significantly upregulated in response to oxidative stress and cigarette smoke exposure, both key environmental triggers in COPD pathogenesis. This suggests a feedback loop in which chronic exposure to irritants perpetuates inflammation through CXCL9-mediated immune recruitment and tissue remodelling [51].

Comparably, IFN-γ induces the production of CXCL10, sometimes referred to as interferon-gamma-induced protein 10 (IP-10), which is produced by a variety of cell types, including dendritic cells, macrophages, and epithelial cells. Th1 cells, natural killer cells, and monocytes are all drawn to inflammatory areas by CXCL10, which functions as a chemoattractant [9]. Increased amounts of CXCL10 are found in the airways and lung tissue of COPD patients. This protein is involved in immune cell recruitment and activation, which intensifies inflammation and tissue damage. Recent evidence suggests that CXCL10 contributes to COPD exacerbations by amplifying neutrophilic inflammation. Unlike CXCL9, which primarily attracts T cells, CXCL10 has been found to promote neutrophil chemotaxis via CXCR3-dependent and independent pathways. This is particularly relevant in acute exacerbations of COPD (AECOPD), where neutrophilic inflammation dominates, leading to increased mucus hypersecretion, airway obstruction, and bacterial colonisation. Targeting CXCL10 with neutralising antibodies has been proposed as a strategy to mitigate AECOPD severity, although clinical trials are still in early stages [52].

Similar to CXCL9 and CXCL10, CXCL11, also known as interferon-inducible T cell alpha chemoattractant (I-TAC), has a similar structure and function. It is initiated by multiple cell types, including endothelial, dendritic, and macrophage cells, and is triggered by IFN-γ. **Table 1** provides a comparative summary of the roles of CXCL9, CXCL10, and CXCL11 in COPD pathogenesis, highlighting their cellular sources, receptors, immune targets, and pathogenic contributions. CXCL11 exhibits a higher binding affinity for CXCR3 compared to CXCL9 and CXCL10, making it a potent chemoattractant for activated T cells in COPD. In addition to its role in Th1-mediated inflammation, CXCL11 has been linked to fibrosis

Table 1. Key differences between CXCL9, CXCL10, and CXCL11 in COPD pathogenesis.

Chemokine	Alternative name	Primary cellular sources	Primary receptor	Key immune cell targets	Pathogenic roles in COPD
CXCL9	Monokine Induced by IFN-γ (MIG)	Macrophages, dendritic cells, epithelial cells	CXCR3	Th1 cells, NK cells	T-cell recruitment, chronic inflammation, airway remodeling
CXCL10	Interferon-Induced Protein 10 (IP-10)	Macrophages, dendritic cells, epithelial cells, fibroblasts	CXCR3	Th1 cells, NK cells, monocytes, neutrophils	Amplifies neutrophilic inflammation, contributes to AECOPD, promotes mucus hypersecretion
CXCL11	Interferon-Inducible T Cell Alpha Chemoattractant (I-TAC)	Endothelial cells, macrophages, dendritic cells	CXCR3	Th1 cells, NK cells, fibroblasts	Enhances T-cell activation, promotes fibrosis, contributes to lung function decline

in COPD by enhancing myofibroblast differentiation and collagen deposition. This dual role in both inflammation and tissue remodelling suggests that CXCL11 inhibition could be a promising approach for reducing lung function decline in COPD patients [53].

Impact of chemokines on chronic inflammation and lung tissue damage

Chemokines have a significant role in the pathophysiology of several inflammatory lung diseases, including pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease (COPD). They have a substantial effect on lung tissue destruction and chronic inflammation. The persistent inflammation in the lungs is caused by the dysregulation of chemokine signalling pathways, which results in tissue damage, remodelling, and compromised lung function. Chemokines play a significant role in lung tissue damage and chronic inflammation by directing the recruitment and activation of immune cells in the lung microenvironment [10]. Chemokines are chemoattractants that guide immune cells, including dendritic cells, neutrophils, macrophages, and T lymphocytes, to regions of inflammation or injury. Once enlisted, these immune cells release pro-inflammatory cytokines, chemotactic factors, and reactive oxygen species, which further damage tissue and initiate the inflammatory cascade. [11].

Chemokines like CCL11 (eotaxin) and CCL5 (regulated on activation, normal T cell produced and released, RANTES), for instance, play a role in drawing eosinophils to the airways in asthma, where they exacerbate hyperresponsiveness and inflammation in the airways. Similar to this, in COPD, chemokines such as CXCL1 (growth-related oncogene-alpha) and CXCL8 (interleukin-8) are essential for attracting neutrophils to the lungs, where they produce proteases and reactive oxygen species, which cause tissue damage and emphysema [12]. Furthermore, by promoting angiogenesis, fibrosis, and airway remodelling, chemokines exacerbate chronic inflammation and lung tissue damage. Chemokines like B lymphocyte chemoattractant (CXCL13) and stromal cell-derived factor-1 (CXCL12) are involved in controlling the migration and activation of myofibroblasts and fibroblasts, leading to the deposition of extracellular matrix proteins and the formation of fibrotic lesions in the lungs. Furthermore, chemokines such as macrophage-derived CCL22 and pulmonary and activation-regulated CCL18 facilitate the recruitment of regulatory T cells and fibrocytes, which support tissue remodelling and fibrosis [13].

Chemokines have global impacts on lung tissue damage and chronic inflammation in addition to local tissue microenvironmental effects. Chemokines secreted by the lungs can reach the bloodstream, resulting in the development of extrapulmonary lung disease symptoms such as metabolic abnormalities, skeletal muscle dysfunction, and systemic inflammation. In patients with inflammatory lung disorders, systemic inflammation adds to the overall illness burden by exacerbating lung tissue destruction and impairing lung function. In brief, in inflammatory lung disorders, chemokines are essential mediators of lung tissue damage and persistent inflammation [14].

Chemokines' role in the pathophysiology of COPD

Vast role of CXCL9 in COPD

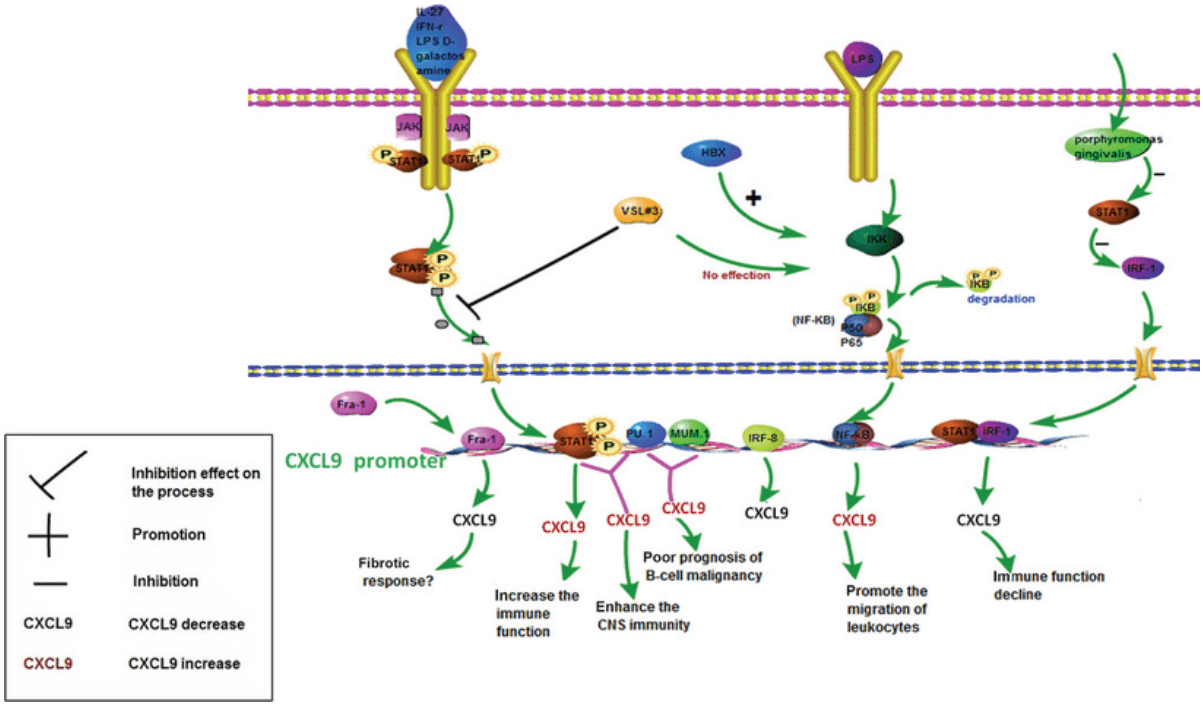
CXCL9, also known as monokine generated by interferon-gamma (MIG), is a chemokine that plays a significant role in the pathogenesis of COPD, or chronic obstructive pulmonary disease. Numerous cell types and inflammatory mediators are involved in tightly regulated mechanisms that produce and regulate it within the lung microenvironment. The primary mechanism that triggers the production of CXCL9 is interferon-gamma (IFN-γ), an essential pro-inflammatory cytokine released by natural killer cells and activated T lymphocytes in response to inflammation or infection. In response to IFN-γ activation, the lungs' macrophages, dendritic cells, and epithelial cells all increase the expression of CXCL9 mRNA and protein [9]. As a result, CXCL9 is released into the surrounding tissue milieu, where it chemoattracts immune cells bearing the expression of its receptor, CXCR3. The degree of inflammation, the presence of other cytokines and chemokines, and the state of immune cell activation in the lungs are a few of the factors that influence the regulation of CXCL9 production in COPD. Patients with COPD who have elevated levels of pro-inflamma-

tory cytokines such as TNF-α and interleukin-1 beta (IL-1β), as well as IFN-γ, are shown to produce more CXCL9 (see **Figure 1**). Moreover, oxidative stress and the activation of the nuclear factor-kappa B (NF-κB) pathway in response to inhaling cigarette smoke increase the production of CXCL9 in COPD [15].

When CXCL9 emerges, it attaches to its receptor, CXCR3, which is expressed on several immune cells, including natural killer cells, T lymphocytes, and dendritic cells, initiating its function. Intracellular signalling cascades triggered by CXCR3 activation are responsible for cell movement, activation, and effector activities. The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K) are examples of these cascades. The interaction of CXCL9 and CXCR3 in COPD is critical for managing the lungs' recruitment and activation of immune cells (see **Figure 1**). For T lymphocytes that express CXCR3, especially T helper 1 (Th1) cells, CXCL9 acts as a chemoattractant. Th1 cells are implicated in the promotion of tissue damage and chronic inflammation in COPD patients [16].

Contribution of other chemokines to COPD progression

In addition to CXCL9, several other chemokines influence the course of Chronic Obstructive Pulmonary Disease (COPD). These chemokines have a crucial role in the recruitment and activation of various immune cells in the lungs, which results in the remodelling of airways, persistent inflammation, and the onset of emphysema. Key immune cells implicated in the pathophysiology of COPD include neutrophils, macrophages, and T lymphocytes. A variety of chemokines mediate their migration to the lungs. Interleukin-8, or CXCL8 (Figure 1), is a strong chemoattractant for neutrophils that is markedly increased in COPD patients' airways, which helps to draw and activate neutrophils in the lungs. Proteases, reactive oxygen species, and cytokines are released by neutrophils, which cause tissue damage, mucus hypersecretion, and airway blockage—all of which advance COPD [17].



IFN-γ, IL-27, D-galactosamine, and so on may all trigger CXCL9 expression via JAK/STAT1, PU.1, MUM1, NF-kB, Fra-1 (direct binding to the CXCL9 promoter), and Egr-1 (uncertain). Additionally, CXCL9 demonstrated a critical involvement in immunological function, including leukocyte, B-cell, and T-cell chemotaxis. JAK, Janus-activated kinase; PU.1, Myeloid Transcription Factor PU.1; MUM1, Multiple Myeloma Oncogene 1; Egr-1, Early Growth Response-1; Fra-1, Fos-related antigen 1; and STAT1, signal transducer and activator of transcription.

Figure 1. Role and Regulation of CXCL9 In COPD (Ding et al., 2016).

Another significant immune system cell group implicated in the pathogenesis of COPD is macrophages. The recruitment and activation of macrophages is caused by chemokines, such as CCL2 (monocyte chemoattractant protein-1) and CCL5 (regulated on activation, normal T cell generated and released, RANTES). Macrophages have a variety of functions in COPD, such as tissue remodelling, pro-inflammatory mediator synthesis, and phagocytosis of pathogens and debris. In COPD, dysregulated macrophage activation is a factor in tissue damage, persistent inflammation, and compromised lung function [18]. The development of emphysema in patients with COPD is linked to T lymphocytes, namely CD8+ cytotoxic T cells. Chemokines that control the recruitment and activation of these cells include CXCL10 (interferon-gamma-induced protein 10) and CXCL11 (interferon-inducible T cell alpha chemoattractant). The increase in airspace that is symptomatic of emphysema and the breach of the alveolar wall are caused by the cytotoxic and pro-inflammatory cytokines generated by CD8+ T cells [19].

Therapeutic targeting of chemokines in COPD

Rationale for targeting chemokines in COPD treatment

Chemokines play a critical role in regulating lung inflammation that is implicated in the pathogenesis of Chronic Obstructive Pulmonary Disease (COPD), which is why treating the condition with an emphasis on chemokines is relevant. Chemokines are essential for immune cell recruitment, activation, and trafficking in the lung microenvironment. They thereby exacerbate tissue damage, persistent inflammation, and diminished lung function in COPD patients. Chemokines are targeted in the therapy of COPD primarily because they are critical for immune cell recruitment to the lungs. As chemoattractants, chemokines guide immune cells to regions of inflammation or injury in the parenchyma and airways of the lung [20]. These cells include neutrophils, macrophages, dendritic cells, and T lymphocytes. These immune cells produce proteases and pro-inflammatory mediators, which cause tissue damage, excessive mucus secretion, and blockage of airways—all of which are factors in the pathophysiology of COPD [21].

Chemokine targeting can be used to modify immune cell trafficking and lower lung inflammation, which can slow down the course of COPD and improve clinical outcomes for patients. Targeting chemokines in COPD treatment has been approached from several angles, including gene therapy, monoclonal antibodies, and small-molecule inhibitors. One method that shows promise for addressing chemokine signalling pathways in COPD is the use of small-molecule inhibitors [22]. By specifically blocking the connection between chemokines and their receptors, these inhibitors stop immune cells from recruiting and activating in the lungs. Targeting chemokine receptors, such as CXCR2 and CXCR3, several small-molecule inhibitors have shown promise in preclinical studies and could be helpful in COPD treatment trials. Another potential method for treating COPD that targets chemokines is the use of monoclonal antibodies. By attaching themselves to particular chemokines or chemokine receptors, these antibodies prevent immune cells from interacting with them and obstruct subsequent signalling pathways. In preclinical models of COPD, for instance, monoclonal antibodies that target CXCL8 and its receptors have demonstrated effectiveness in lowering inflammation and enhancing lung function [23]. A promising strategy for regulating chemokine expression in COPD is gene therapy. Gene constructs expressing chemokine inhibitors or decoy receptors can be introduced into the lung to control chemokine levels locally and reduce lung parenchymal and airway inflammation. Gene therapy has the potential to deliver therapeutic molecules locally and sustainably, reducing systemic side effects and increasing treatment efficacy for COPD patients.

Overview of current therapeutic strategies for COPD

The hallmarks of Chronic Obstructive Pulmonary Disease (COPD), a chronic lung condition, are airflow limitation, persistent inflammation, and structural changes in the lung parenchyma and airways. Despite advances in our understanding of the biology of COPD, the disease still has a significant worldwide influence on public health and has few therapeutic choices. Reducing symptoms, decreasing the frequency of exacerba-

tions, improving quality of life, and delaying the progression of the condition are the objectives of current COPD treatment strategies. These strategies integrate non-pharmacological and pharmaceutical interventions that are tailored to each patient's needs in an interdisciplinary way [24]. Reduced airway inflammation, bronchospasm, and mucus hypersecretion are the main goals of pharmacological therapies for COPD because these conditions play a significant role in the onset and progression of the disease. Bronchodilators, such as beta2-agonists and anticholinergics, which lower smooth muscle tone and improve airflow dynamics in the airways to ease symptoms, are first-line therapy for COPD symptoms. Long-acting bronchodilators offer continuous bronchodilation when taken in conjunction with inhalation devices; these drugs are recommended for maintenance therapy in patients with COPD who have recurrent symptoms [25]. In addition to bronchodilators, anti-inflammatory drugs such as inhaled corticosteroids (ICS) are frequently used to treat COPD, especially in those with a history of exacerbations and eosinophilic inflammation. ICS reduce airway inflammation, lessens the likelihood of aggravation, and inhibits the production of pro-inflammatory cytokines and chemokines, all of which have anti-inflammatory effects, for COPD patients with moderate to severe disease. Combination therapy, which combines long-acting bronchodilators with ICS, is frequently recommended to maximise symptom control and prevent exacerbations [26].

The pharmacological medicines known as phosphodiesterase-4 (PDE4) inhibitors are an additional class that has been approved for the management of COPD. PDE4 inhibitors, particularly roflumilast, work by preventing immune cells from breaking down cyclic adenosine monophosphate (cAMP), which lowers the release of pro-inflammatory mediators and lessens airway inflammation. Patients with substantial airflow limitation and a history of exacerbations despite receiving optimum bronchodilator therapy are recommended to use roflumilast. Non-pharmacological therapies, which include pulmonary rehabilitation, supplementary oxygen therapy, and lifestyle adjustments, are essential parts of managing COPD [27]. For COPD patients, quitting smoking is the single most effective intervention for slowing the development of the disease and lowering death. Programs for pulmonary rehabilitation, which include education, exercise training, and psychological support, help individuals with COPD improve their quality of life, exercise capacity, and dyspnea. For COPD patients with severe hypoxemia, supplemental oxygen therapy is advised to reduce symptoms and enhance exercise tolerance [28].

Drug development and repurposing efforts

Development of chemokine receptor inhibitors

The identification of chemokine receptor inhibitors represents a significant breakthrough in drug development and repurposing, particularly for chronic inflammatory diseases such as Chronic Obstructive Pulmonary Disease (COPD). A viable treatment approach to control the inflammatory environment and lessen illness symptoms is to target these receptors. The development of chemokine receptor inhibitors was justified by their capacity to specifically inhibit the interaction between chemokines and their receptors, obstructing subsequent signalling cascades that result in the recruitment and activation of immune cells [29]. Due to their involvement in inflammation associated with COPD, several chemokine receptors, including CXCR2, CXCR3, and CCR5, have been identified as possible targets. For example, CXCR2 is a receptor for chemokines like CXCL1 and CXCL8, which are essential players in the migration of neutrophils to the lungs. By blocking CXCR2, tissue injury and inflammation can be lessened by decreasing neutrophil influx and the subsequent release of proteases and ROS [30].

Chemokine receptor inhibitor development has moved through several phases, including preclinical research and clinical trials. These inhibitors are effective in lowering inflammation and enhancing lung function in preclinical models of COPD. In animal studies, for instance, CXCR2 inhibitors have demonstrated encouraging outcomes by reducing neutrophil infiltration and reducing airway hyperresponsiveness. Clinical trials to assess the safety and effectiveness of chemokine receptor inhibitors in humans have been made possible by these results. Sev-

eral chemokine receptor inhibitors are presently being evaluated clinically for inflammatory illnesses such as COPD [9]. A prominent example is the CXCR2 antagonist AZD5069, which has been studied in clinical trials for COPD. Early-phase trials indicate that AZD5069 is well-tolerated and may be used as a treatment agent for COPD since it successfully lowers lung neutrophilic inflammation. Other CXCR2 inhibitors, including MK-7123, have shown promise in clinical studies, indicating that targeting this receptor may have therapeutic benefits [31].

Apart from creating new chemokine receptor inhibitors, attempts are still on to repurpose current medications for the treatment of COPD. By finding new therapeutic applications for already-approved medications, drug repurposing helps to cut costs and speed up the development of new medicines. For example, Maraviroc, which was first created as a CCR5 antagonist for the treatment of HIV, has demonstrated promise in controlling immune responses and lowering inflammation in COPD patients [32]. One example of how current medications can be used to address unmet medical needs in chronic inflammatory illnesses is the repurposing of Maraviroc for COPD. Chemokine receptor inhibitor development and repurposing also require resolving several issues, including maximising drug delivery, reducing off-target effects, and guaranteeing long-term safety. To increase the local concentration of chemokine receptor inhibitors in the lungs and minimise systemic exposure, inhalation administration devices are being investigated as a potential means of optimising therapeutic efficacy. Furthermore, current studies seek to increase these inhibitors' selectivity to lessen side effects and improve their safety profile [33].

Drug repurposing

Drug repurposing is a cutting-edge method of drug research that involves developing new therapeutic uses for pharmaceuticals that have already received approval. This method has numerous advantages in this regard. Safe and efficient treatments for long-term illnesses such as Chronic Obstructive Pulmonary Disease (COPD) are always in demand. Drug repurposing lowers the time, expense, and risk associated with conventional drug development pathways by making use of the established pharmacological profiles, safety information, and manufacturing procedures of already approved medications [34]. Because COPD is a complicated illness involving immunological responses, tissue remodelling, and intricate inflammatory processes, there is justification for drug repurposing in its therapy. With numerous medications now on the market and a wealth of clinical experience behind them, researchers can narrow down those whose mechanisms of action have the potential to impact the pathophysiology of COPD positively. This strategy may open up new therapeutic avenues that weren't previously thought of while these medications were being developed [34].

A noteworthy instance of repurposing drugs for COPD is the application of inhibitors of phosphodiesterase-4 (PDE4). PDE4 inhibitors have proven to help reduce COPD exacerbations and inflammation. They were initially created to treat conditions including rheumatoid arthritis and asthma because of their anti-inflammatory and immunomodulatory properties. PDE4 inhibitor rolumilast is now a licensed treatment for COPD, with an emphasis on individuals with severe disease and a history of recurrent exacerbations [35]. The efficacy of roflumilast highlights the possibility of repurposing medications with well-understood mechanisms of action to fill gaps in COPD treatment. Repurposing statins, which are typically utilised for their ability to decrease cholesterol in cardiovascular illnesses, is another example. Due to their anti-inflammatory and immunomodulatory qualities, statins have sparked research into possible COPD benefits. Due to their impact on systemic inflammation, clinical trials have revealed that statins may improve overall outcomes and lessen the frequency of COPD exacerbations. Statins represent the promise of repurposing well-established medications to take advantage of their pleiotropic effects in treating chronic inflammatory illnesses like COPD, despite the inconsistent outcomes and need for additional research [36].

Azithromycin and other macrolide antibiotics have been repurposed for the treatment of COPD. In addition to their antibacterial properties, macrolides have immunomodulatory and anti-inflammatory properties. It has been demonstrated that long-term low-dose azithromycin treatment lowers the incidence of exacerbations in COPD patients. This effect is probably due to alterations

in inflammatory pathways and a decrease in bacterial colonisation of the airways. Azithromycin's newfound use in the treatment of COPD has given patients another therapeutic option, especially those who have a chronic bronchitis phenotype and a history of exacerbations [37]. Profiting from advances in disease biology is another benefit of drug repurposing. For example, biologics that were first created for other inflammatory diseases are now being investigated for COPD. Treatment for COPD has shifted from asthma to monoclonal antibodies that target cytokines linked to eosinophilic inflammation, such as interleukin-5 (IL-5) or interleukin-13 (IL-13). Mepolizumab and benralizumab, for example, were first licensed for the treatment of severe eosinophilic asthma. Currently, clinical trials are being conducted to evaluate the effectiveness of these drugs in COPD patients who exhibit eosinophilic phenotypes. This illustrates how knowledge from one illness can influence treatment approaches in another [38].

The repurposing of drugs is not without difficulties. Significant obstacles include those related to intellectual property, regulations, and the requirement for strong clinical data to support new indications. Furthermore, the dosage, mode of administration, and any adverse effects of the repurposed medicine need to be carefully considered in light of the latest therapeutic application. Despite these difficulties, medication repurposing is a tempting way to increase the range of treatments available for COPD and other chronic illnesses due to the time and money savings as well as the possibility of significant clinical advantages [34].

Clinical trials and future research

Clinical trials provide the foundation for developing new medicines and establishing their safety and efficacy in the treatment of illnesses like chronic obstructive pulmonary disease (COPD). Numerous clinical trials have looked into the possibility of different chemokine inhibitors to address the immunological dysregulation and chronic inflammation that are hallmarks of COPD, either as monotherapy or in conjunction with traditional therapies. These trials have been conducted in the last few years. Targeting chemokine pathways is becoming increasingly popular, according to an overview of recent clinical trials. Trials involving CXCR2 inhibitors, including danirixin and navarixin, have demonstrated encouraging outcomes. The goal of these inhibitors is to prevent neutrophil recruitment, which is a significant cause of inflammation associated with COPD [39]. Research has indicated that these medications can enhance lung function and lower inflammatory markers in sputum, while their effects on the frequency of exacerbations have varied. While some trials found no discernible benefits when compared to placebo, others showed a decrease in the frequency of exacerbations. These contradictory findings demonstrate the complexity of COPD and the need for more improvement in medication targeting and patient selection [40].

Clinical trials have also focused on monoclonal antibodies that are directed against chemokines or their receptors. For example, COPD patients who experience frequent exacerbations have been screened for the anti-CXCL8 antibody, which neutralises the chemokine responsible for neutrophil recruitment. Early-stage studies demonstrated that this antibody could enhance specific clinical outcomes and lower lung neutrophil levels. Large-scale trials are yet required to validate these advantages and ascertain the medicines' long-term safety profile [41]. Combination therapies using chemokine inhibitors and conventional COPD medications have been investigated in addition to monotherapy. Studies involving CXCR2 inhibitors in combination with long-acting bronchodilators and inhaled corticosteroids (ICS) have demonstrated that the addition of a chemokine inhibitor can further enhance the anti-inflammatory benefits of conventional therapies. By treating the underlying inflammation as well as the symptoms of COPD, these combination therapies seek to offer a more thorough method of controlling the condition. According to preliminary findings, these combinations are more successful than standard medications alone at improving lung function and lowering exacerbation rates [42].

Many important factors must be taken into account while designing clinical trials for COPD medicines to ensure reliable and significant outcomes. The gold standard for determining the effectiveness and safety of novel drugs is still randomised controlled trials (RCTs). Usually,

these studies have several arms, such as a placebo group and one or more treatment groups that receive various dosages of the experimental medication. The use of substitute controls provides a clear comparison and an accounting for the placebo effect, which is necessary to evaluate the actual impact of the new medication [43]. Patient selection is a crucial component of COPD clinical trial design. With diverse phenotypes, including differing degrees of neutrophilic and eosinophilic inflammation, COPD is a heterogeneous illness. Using biomarkers, like sputum neutrophil levels or blood eosinophil counts, to stratify patients can improve clinical trial precision by identifying patient subgroups more likely to react to particular treatments. This tailored strategy can lower trial result variability and raise the chance of finding meaningful treatment benefits [44].

Further research needs

Further COPD research is required to meet several essential criteria and further our understanding of this complex illness and its management. Primarily, additional investigation is needed to comprehend the fundamental mechanisms of COPD pathogenesis, particularly concerning the role of chemokines and their interactions with immune cells. Clarifying the precise pathways via which chemokines cause lung tissue damage and persistent inflammation will lay the groundwork for the development of more specialised and potent treatments. More investigation is required to find trustworthy biomarkers that can forecast the course of the disease, the likelihood of an exacerbation, and the effectiveness of therapy in COPD patients, in addition to mechanistic research [6]. Though they are somewhat utilised now, biomarkers like sputum neutrophil counts, blood eosinophil counts, and inflammatory cytokines still need to be validated and standardised for usage in various patient populations and therapeutic contexts. Strong biomarkers will enable customised medicine strategies, enabling medical professionals to customise patient regimens according to unique patient profiles [45].

Clinical research ought to concentrate on improving treatment approaches, such as chemokine inhibitors and combination therapy dosage and duration. Comprehensive long-term follow-up randomised controlled trials (RCTs) are necessary to validate the safety and effectiveness of new treatments and determine how best to use them to treat various COPD phenotypes. Research on comparative efficacy can help clarify the relative advantages of multiple treatment modalities and direct clinical judgment. Studies that examine the long-term effects of COPD therapy beyond symptom management and the reduction of exacerbations are also necessary [46].

Collaboration between researchers, doctors, pharmaceutical companies, and regulatory bodies is necessary to address these research demands. To expedite the development of more potent COPD treatments, multidisciplinary strategies that incorporate basic science, translational research, and clinical trials will be essential. Additionally, encouraging global cooperation and data-sharing programs can make it possible to include bigger and more diverse study populations, which will improve the generalizability of research findings and hasten the integration of new knowledge into clinical practice [47]. Ultimately, consistent funding support and prioritised research efforts to meet the various hurdles presented by this crippling disease are necessary to advance research on COPD. The field can significantly improve patient outcomes and lessen the worldwide burden of COPD by giving priority to these research requirements [48].

Conclusions

The numerous functions that chemokines play in the pathogenesis of chronic obstructive pulmonary disease (COPD) and their potential as targets for treatment are examined in this research. Chemokines are essential for immune cell recruitment, the maintenance of chronic inflammation, and the unique anatomical abnormalities in the lungs associated with COPD. Numerous studies have been conducted on important chemokines, such as CXCL8, CXCL9, CXCL10, and CXCL11, demonstrating their diverse functions in controlling inflammatory responses and influencing disease progression [22]. Chemokine targeting as a therapeutic approach is a viable way to reduce inflammation associated with COPD and enhance clinical results. Preclinical research and clinical

trials are providing new information about the effectiveness of biologics and chemokine inhibitors in lowering exacerbation rates, improving lung function, and even altering disease course.

Furthermore, combination medicines that include chemokine inhibitors and conventional COPD medications have demonstrated synergistic results, providing a multimodal approach to managing this complex disease [49]. Even though there has been significant progress, there are still several obstacles to overcome and areas that need more research. Subsequent investigations ought to clarify the exact processes by which chemokines contribute to the pathophysiology of COPD, verify biomarkers that forecast treatment outcomes, and refine therapy approaches via novel medication development and personalised medicine methods. Long-term research is also required to evaluate the sustainability of treatment effects and any potential safety issues related to continued usage of chemokine-targeted medicines [50]. By bridging these knowledge gaps and utilising multidisciplinary teamwork, the field can progress toward more efficient, customised COPD treatments. Translating scientific findings into tangible improvements in patient care and outcomes will require sustained investment in translational research, strong clinical trials, and data-driven insights. Ultimately, there is hope for reducing the impact of COPD on individuals, healthcare institutions, and society at large through the continued exploration of novel strategies to target chemokines.

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Conflicts of Interest
The authors declare that they have no conflicts of interest in this work.

Ethical Statement
This study does not contain any studies with human or animal subjects performed by any of the authors.

Data Availability Statement
The data that support this work are available upon reasonable request to the corresponding author.

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