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Review

Role of Inflammatory Mediators in Chronic Obstructive Pulmonary Disease Pathogenesis: Updates and Perspectives

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Abstract: Chronic obstructive pulmonary disease (COPD) is a chronic, debilitating condition that affects the lungs and airways. It is characterized by persistent bronchitis, a condition exemplified by the inflammation of the bronchial tubes, the hypersecretion of mucus, emphysema, and the destruction of the airway parenchyma. The combination of these conditions leads to persistent tissue damage, pulmonary fibrosis, and ongoing inflammation of the airways. The inflammatory response in COPD is a complex process that is orchestrated by a wide range of immune cells. These include lung epithelial cells, monocytes, macrophages, neutrophils, eosinophils, and T and B lymphocytes, among others. These cells work together to produce a wide range of inflammatory biomarkers that are involved in the pathogenesis of COPD. Some of the key inflammatory biomarkers that have been identified in COPD include a variety of cytokines, the C-reactive protein/serum albumin ratio, fibrinogen, soluble receptor for advanced glycation endproducts, club/clara cells in the lungs with a molecular weight of 16 kDa, surfactant protein D, adiponectin, reactive oxygen species, and proteases. This review aims to provide a comprehensive overview of the role of immune cells and key inflammatory biomarkers in the development and progression of COPD. It will delve into the intricacies of the inflammatory response in COPD, exploring the various cell types and biomarkers that are involved in this process. By understanding the underlying mechanisms that drive COPD, we can better develop targeted treatments that can help to alleviate the symptoms of COPD.

Keywords: cytokines; chronic obstructive pulmonary disease; inflammation; oxidative stress; immune response

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health challenge that kills more than 3 million people annually [1,2]. While there have been significant developments in the cellular and molecular understanding of asthma, COPD has been comparatively neglected, and no therapies are available that reduce the progression of

the disease. Despite its worldwide importance, due to the complexity of the disease, the heterogeneity of patient populations, the limited understanding of the underlying mechanism, and a lack of active research at the molecular level, there have been few advances in COPD research at cellular and molecular levels [3–6].

COPD is a poorly irreversible condition with high morbidity and mortality rates. It is characterized by bronchiolitis, emphysema, mucus hypersecretion, and obstructive bronchiolitis, which are its major pathological hallmarks [7,8]. The loss of small airways is a common symptom of illness and an early indicator of a disease with progressive airway obstruction. The illness phase is characterized by emphysematous deterioration of the small airway compartment and a lack of elastic recoil [9]. Epidemiological studies indicate that COPD is more prevalent in the elderly than in younger individuals [10]. According to GOLD (Global initiative for chronic obstructive lung disease), COPD severity is divided into four grades (grade I: mild, grade II: moderate, grade III: severe, and grade IV: highly severe) as per the health condition of the patient (Figure 1) [11]. While smoking is still a major contributor, other factors are also being given increasing attention. Smoking-induced pulmonary damage with a potent inflammatory response is responsible for the progression of COPD. The accumulation of air pollutants, such as cadmium and manganese, in the lungs may serve as a contributing factor in advanced COPD [12,13]. In addition to air pollutants, respiratory infections are also considered a major contributor to inflammation in COPD.

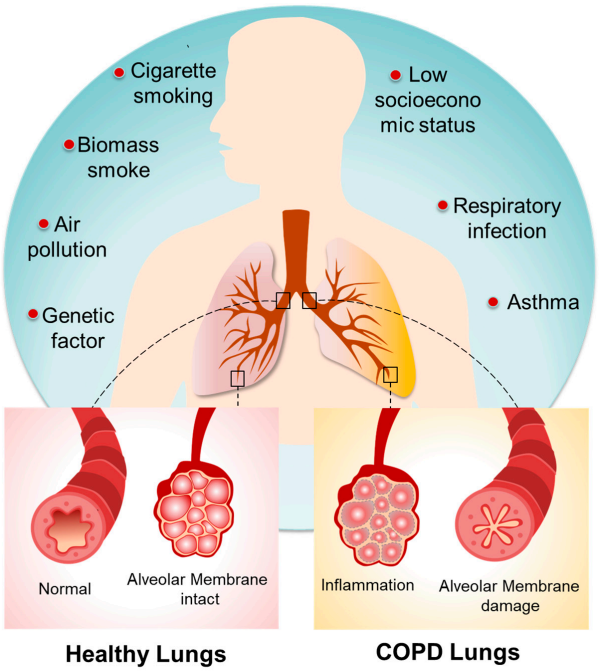
Ferritin, a ubiquitous intracellular protein, plays a central role in iron storage and homeostasis, and its serum levels are widely used as clinical markers of total body iron stores [14]. However, ferritin is also an acute-phase reactant, meaning that its concentration increases in response to inflammation, infection, and other systemic stressors, potentially confounding its interpretation in individuals with chronic inflammatory conditions such as COPD. The challenges in accurately assessing iron status using ferritin in the context of inflammation are significant, as elevated ferritin levels may mask concurrent iron deficiency, leading to the underdiagnosis and undertreatment of this condition. In the context of COPD, the disruption of iron homeostasis is further complicated by the inflammatory nature of the disease [14]. The inflammatory processes in COPD, characterized by elevated levels of circulating cytokines, can lead to the sequestration of iron within the reticuloendothelial system, limiting its availability for erythropoiesis and other essential metabolic processes. This phenomenon, known as anemia of chronic inflammation, is frequently observed in COPD patients and can exacerbate respiratory symptoms, reduce exercise capacity, and impair overall quality of life [6,14].

Systemic and local inflammatory responses make a crucial contribution to the progress of COPD [15]. Innate and adaptive immune system-associated factors are responsible for the pulmonary inflammatory response in COPD [16]. In many COPD cases, the inflammatory phenotypes are primarily associated with eosinophilic and neutrophilic inflammation [17]. Eosinophilic COPD is often responsive to corticosteroid therapy, while neutrophilic COPD, the more prevalent phenotype, is typically associated with poor corticosteroid responsiveness and persistent inflammation. This immune heterogeneity highlights the complexity of COPD pathogenesis and its clinical management. Despite the availability of anti-inflammatory therapies, including inhaled corticosteroids and phosphodiesterase-4 inhibitors, their effectiveness remains limited, particularly in patients with neutrophilic inflammation [18]. These therapeutic limitations highlight the need for a more nuanced understanding of inflammatory mechanisms. In this context, inflammatory mediators play a central role in orchestrating the immune response and driving disease progression, making them promising targets for improved diagnostic and therapeutic strategies. Evidence suggests that the expression of inflammatory mediators and oxidative

stress markers is raised in the peripheral blood of COPD patients [19]. In COPD patients, a small airflow blockage may occur due to the infiltration of macrophages and neutrophils, $CD4^+$ cells, $CD8^+$ cells, and B cells, leading to the expression of inflammatory molecules [20]. In COPD, the majority of the inflammatory mediators are cytokines and related proteins [19,21]. Cytokines include a large family of extracellular secretory proteins, produced by a range of cells involved in innate and adaptive immunity [22]. Cytokines play an essential role in cell growth, activation, differentiation, proliferation, cell-to-cell interaction, and cell migration [23–25]. Cytokines are produced in groups with distinct patterns and have overlapping functions. These mediators bind to their cognate receptors, present on the surface of the cell, and activate intracellular signaling pathways [26]. The signal activation results in an increase in their expression as well as the expression of target genes [14,27]. The methodology we used for the literature review was consistent, identifying relevant and impactful scientific articles on COPD. It involved a systematic review using various databases, such as Google Scholar, PubMed, Science Direct, and Scopus. This review highlights key factors, cellular and molecular mediators of pulmonary inflammation, and their role in COPD pathogenesis. Deep insight into the significance of inflammatory biomarkers at the molecular level may contribute to the advancement of approaches and methods for the diagnosis and management of COPD.

2. Factors Influencing the Inflammatory Response in COPD

The key factors influencing COPD include smoking, genetic factors, aging, air pollution, and respiratory infections (Figure 1) [28]. These factors are responsible for triggering immune cells and the expression of inflammatory biomarkers.



Patient condition	Grade	FEV (Forced expiratory volume in 1 s)	FEV1/FVC *
Mild	GOLD 1	≥80% of expected	<0.7
Moderate	GOLD 2	<80% ≥50%	<0.7
Severe	GOLD 3	<50% ≥30%	<0.7
Very severe	GOLD 4	<30% or <50% with right side heart failure or failure in respiratory system	<0.7

Figure 1. Contributing factors and pathological manifestations in COPD: a schematic representation of factors and inflammatory response in the pulmonary alveolar membrane in COPD with a standard GOLD criterion [29]. * FEV1: forced expiratory volume in 1 sec, FVC: forced vital capacity.

2.1. Cigarette Smoking

Cigarette smoking kills nearly 480,000 people in the United States per year and the number of deaths exceeds the total number of persons who die due to the human immunodeficiency virus (HIV) infection, drug addiction, and alcohol abuse [30]. Cigarette smokers are at high risk of developing COPD [31]. A strong connection between cigarette smoking and COPD has been scientifically proven; non-smokers still account for 1/4th and 1/3rd of COPD cases [32]. Research has shown that people with high risk of genetic disease are more susceptible to COPD when exposed to smoking [33]. The progression of COPD is also aligned with programmed cell death and inflammation associated with smoking. Whole-genome transcriptomics analysis of blood monocytes from smokers and non-smokers indicates that inflammation and apoptosis contribute to COPD [34]. A research study on smokers in the Greenland Seafood Industry found that smokers were more likely to develop COPD and CB (chronic bronchitis), indicating a clear link between smoking and COPD [35]. Evidence suggests that there is an established correlation between cigarette smoking and COPD. Cigarette smoke contains toxic and mutagenic chemicals that lead to lung damage and impair the regulatory framework of the cells. This may result in severe cell damage and an unregulated chronic inflammatory response, increasing the likelihood of COPD progression in chronic smokers [36–40].

2.2. Genetic Factors

According to the findings of the research, COPD has been linked to genetic factors. The absence of alpha-1 antitrypsin is an autosomal recessive condition that affects lung function in patients [41,42]. SERPINA1 and a 12.2 kb gene on chromosome 14 (14q31–32.3) encode alpha-1 anti-trypsin [43]. The key role of an anti-trypsin molecule is to regulate the function of proteases during the pulmonary immune response [44]. This condition may afflict young individuals, who may develop severe COPD leading to terminal respiratory insufficiency and possible premature death. In addition, genes associated with vitamin D-binding protein, alpha1-antichymotrypsin, alpha2-macroglobulin, and blood group antigens have been linked with COPD development and progression [33]. Genetic alterations may contribute to the loss of a key regulator function, thereby increasing the susceptibility to COPD [45,46].

2.3. Accelerated Aging

Aging is characterized by time-dependent structural and functional changes in an organism. COPD is generally considered a disorder of elderly people, and proof suggests that emphysema occurs due to increased lung parenchymal aging [47]. The pathophysiology of normal aging and pulmonary emphysema is similar, with an increase in alveolar space and a decrease in elastic rebound. The reduced expression of Sirtuin 1 (SIRT1) has also been identified in endothelial progenitor cells, endothelial progenitor cells, cellular senescence, and circulation endothelial progenitor cells of elderly COPD patients [48]. Moreover, four age-related genes (CDKN1A, HIF1A, MXD1, and SOD2) were highly expressed in clinical COPD samples as well as in cigarette smoke extract-exposed Beas-2B cells [49]. These genes play an important role in apoptosis, cytokine expression, and antioxidant activity. CDKN1A encodes a cyclin-dependent kinase inhibitor, essential for DNA repair [50]. HIF1A controls cellular and developmental responses to hypoxia [51]. MXD1 (MAX dimerization protein 1) regulates cellular apoptosis, proliferation, and differentiation [52]. SOD2 (superoxide dismutase 2) protects cells against oxidative damage [53]. Cellular senescence or aging may have a direct link with the progression of COPD. Given the fact that aging may contribute to high mutation rates and ineffective cellular DNA repair processes, the risk of COPD is greater in elderly adults than in younger individuals [54–56].

2.4. Air Pollution

Air pollution is a serious challenge for public health worldwide. It contributes to the high burden of respiratory diseases, leading to high morbidity and mortality [57]. Air pollution exposure and COPD morbidity have been studied extensively [58]. High levels of O_3 [59], NO_2, SO_2 [60], and $PM_{2.5}$ [61] can increase the death risk in COPD patients. Studies have shown that the long-term effect of $PM_{2.5}$ exposure may cause lung function to deteriorate and aggravate COPD symptoms [62]. Lung function is directly affected by air pollution. Air pollutants may target a wide range of molecular pathways in the pulmonary cells to promote cellular damage and persistent inflammation. Thus, the probability of developing COPD is higher in regions with high pollution levels compared to less polluted areas [63,64].

2.5. Respiratory Infection

Lungs possess innate and adaptive immune strategies to fight against infectious diseases [65]. Therefore, compared to upper respiratory tract infections in healthy persons, lower respiratory infections are comparatively uncommon. However, both acute and chronic lower respiratory tract infections are more common in COPD patients. Some 50% of COPD lungs may carry potentially dangerous infectious bacteria in the pulmonary airways [66]. These infections are a serious comorbidity in COPD because they have a considerable impact on the clinical course of the illness. Exacerbations of COPD are now firmly connected to recurrent acute infections by bacterial and/or viral pathogens. The microbiome study of 1,706 sputum samples from 510 COPD patients showed that *Haemophilus influenzae* was the most common bacteria in COPD patients [67]. Even though studies showed a link between COPD and pulmonary infection, the direct significance of infections in acute exacerbations is still unclear and uncertain. Non-typable *H. influenzae* is a commensal in healthy individuals but, in COPD patients, it can cause serious bronchial infections [68,69]. During exacerbations, the number of bacteria increases, disrupting the equilibrium. This initiates a potent inflammatory response. Immune mediators can disrupt mucosal immunity which may in turn help pathogens and lead to chronic infection. The long-term effects of infection may cause serious inflammatory damage to the lungs of COPD patients. Another key pulmonary infectious bacteria, *Pseudomonas aeruginosa*, a major pathogen of lung infection in cystic fibrosis, has also been associated with pulmonary infections in COPD patients [66]. Additionally, research has also shown the importance of *Aspergillus* species as a fungal pathogen in COPD [70]. Additional studies have also outlined the interrelationship between COVID-19 and COPD concerning impaired lung functions, susceptivity to viral infection, and high comorbidities [71]. Pulmonary infections are more prevalent in COPD patients, which suggests that they may have a significant role in the progression or worsening of COPD symptoms. Infections have a direct effect on our immune system, resulting in the massive production of pro-inflammatory mediators. Hence, pulmonary infections may contribute to the advancement of COPD, rather than its onset [72,73]. Overall, the details of factors influencing COPD are presented in Table 1.

Table 1. Characteristics of potential factors and molecular markers.

Potential Factors	Characteristics/Agent	Changes in Lungs/Cells	Molecular Markers/Analysis	References
Cigarette smoking	Programmed cell death and inflammation in lung cells	Apoptosis, immune response, cell adhesion, and inflammation	A whole-genome transcriptomics analysis of blood monocytes (principal component analysis and hierarchical component analysis performed for genes CASP9 and TNFRSF1A)	[34]
	Chronic bronchitis	Inflammation and lung injury. Toxic and mutagenic chemicals that impair regulatory framework of the cells	COPD diagnosis relies on the FEV1/FVC ratio post-bronchodilator set by the Global Lung Function Initiative	[35]
Genetic	Lung function impairment in COPD patients	Terminal respiratory insufficiency and lung injury	Alpha-1 antitrypsin deficiency (imbalances in protease–antiprotease protection in the lung)	[41,42]
Accelerated aging	Cellular senescence in lung cells	Increase in alveolar space and a decrease in elastic rebound	The effect was assessed by examining DNA double-strand breaks and senescence levels in BOEC from smokers and COPD patients compared to healthy nonsmokers. Changes in the Sirtuin 1 (SIRT1) expression	[48]
	Aged and young pulmonary cells exposure to cigarette smoke	Increased expression of age-related genes, regulating apoptosis, cytokine expression, and antioxidant activity	Aging-related genes in COPD were investigated using bioinformatic analyses, identifying 24 candidate genes enriched in cytokine activity, apoptosis, NF-κB, and IL-17 signaling, with four genes (CDKN1A, HIF1A, MXD1, and SOD2)	[49]
Air pollution	Long-term ozone exposure, and $PM_{2.5}$ exposure	Pollutants cause lung function to deteriorate and aggravate the COPD symptoms	Pollutant-induced inflammatory cytokine expression	[59–61]
Respiratory infection	*Haemophilus influenzae*	Bronchial infections elevated sputum IL-1β and tumor necrosis factor α	1706 sputum samples from 510 COPD patients were integratively analyzed, using COPDMAP/AERIS as discovery sets and BEAT-COPD for validation.	[67]
	Pseudomonas aeruginosa	Biofilm formation in COPD lungs	Analysis of sputum samples and recommendations for antibiotic treatment in stable COPD with chronic bronchial infection	[66]
	Aspergillus sp.	Lung cell infection	Overview of clinical Aspergillus signatures in COPD and bronchiectasis, covering advances in understanding the mycobiome using next-generation sequencing	[70]
	COVID-19	Impaired lung functions	Evidence indicates that COVID-19 outcomes are exacerbated in COPD patients	[71]

3. Role of Immune Cells in COPD

The lungs are vital immune organs that use both innate and adaptive immune cells to generate a robust immune response. A compromised pulmonary immune system contributes to the development and progression of COPD. Pulmonary immune cells are responsible for the production of ROS (reactive oxygen species), chemokines, cytokines, and proteases in COPD (Figure 2) [74]. It has been observed that activated macrophages, neutrophils, T lymphocytes, and dendritic cells promote potent inflammatory responses in COPD [75]. Furthermore, COPD macrophages are more inflammatory than those in non-COPD patients, which leads to a persistent inflammatory response. Additionally, COPD-associated macrophages have a reduced ability to phagocytose *H. influenzae*, which may result in lung infection and airway colonization [76]. Even though the involvement of immune cells is well documented, there is still a huge gap in the comprehensive understanding of accurate cellular profiling in COPD lungs. This section discusses the involvement of immune cells in the pathophysiology of COPD.

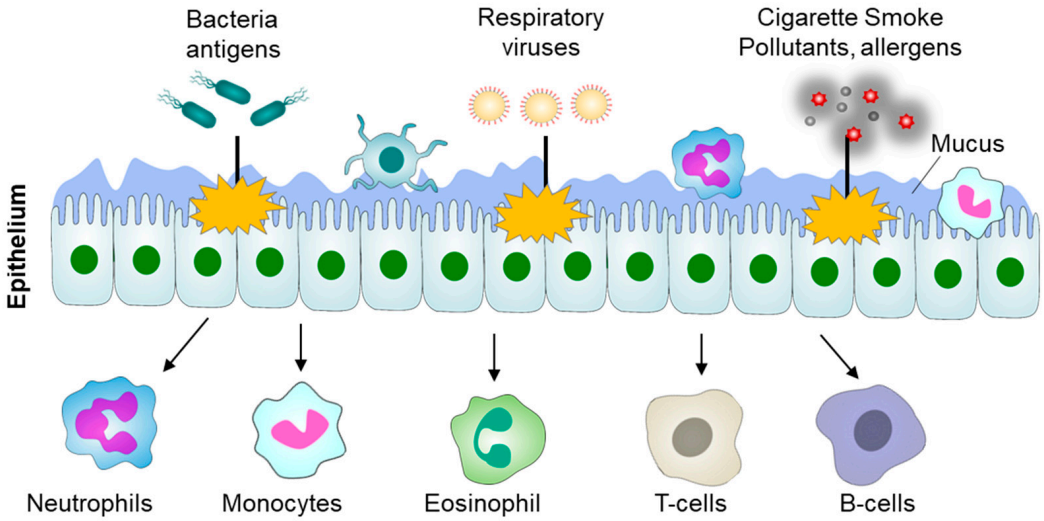


Figure 2. Immune cell and inflammatory cell recruitment in COPD lungs: activation of major inflammatory cells against smoke, toxins, and bacterial and viral infection in COPD.

3.1. Neutrophils

Neutrophils account for around 70% of white blood cells (WBCs) and are widely recognized as a critical component of innate immunity [77]. In COPD, neutrophils are present in the lung airways of COPD patients [77]. In response to hypoxia and inflammation, the neutrophil count and their half-life increase [78]. Research also showed that reduced neutrophil migration may result in protease-induced tissue damage in COPD lungs [79]. A neutrophilic rise in bronchial biopsies and airways is linked with acute exacerbation [80]. Neutrophils induce the release of oxidants and serine proteases [81]. Evidence of neutrophil priming has been observed in COPD patients [82]. Priming is an important initial step for neutrophil stimulation and the production of inflammatory mediators. There are several neutrophilic recruitment signals, including IL-8, and CXC chemokines are detected in COPD airways [83]. In addition to neutrophils, the role of monocytes, eosinophils, and T-lymphocytes has been observed in COPD patients [73,84].

3.2. Macrophages

Macrophages play a central role in the development and progression of COPD by regulating inflammation, immune responses, and tissue remodeling [85]. These cells release a wide array of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and

IL-8, promoting the recruitment of neutrophils and sustaining chronic inflammation [86]. Macrophages also produce reactive oxygen species (ROS) and proteolytic enzymes such as matrix metalloproteinases (MMPs), contributing to alveolar damage and emphysema. In COPD patients, skewed polarization towards the M1 phenotype (pro-inflammatory) over the M2 phenotype (anti-inflammatory/tissue repair) further drives tissue injury [87]. Additionally, macrophages in COPD exhibit impaired phagocytic capacity, reducing their ability to clear pathogens and apoptotic cells, which exacerbates inflammation. These dysfunctional responses are amplified by chronic exposure to cigarette smoke and pollutants, altering key signaling pathways such as NF-κB and STATs. Overall, macrophages in COPD exhibit a hyperactive yet inefficient immune profile that contributes to persistent inflammation and impaired resolution, making them potential targets for future therapeutic strategies [85–87].

3.3. Monocytes

Monocytes are involved in antigen presentation, phagocytosis, cell migration, cytokine secretion, apoptosis, and differentiation [88]. Alveolar epithelial cell death-driven lung tissue damage is a hallmark of COPD etiology. The epithelial cells in the lungs suffer inflammatory monocyte-driven ferroptosis [89]. Ferroptosis is characterized by iron-dependent lipid peroxidation and is found to be the most common cell death mechanism [90,91]. Tőkés-Füzesi et al. [92] showed that the membrane vesicles shed by monocytes are increased in COPD exacerbation. Monocyte chemotactic protein-1 is responsible for the high level of monocytes in the bronchoalveolar lavage and sputum of COPD patients [93].

3.4. Eosinophils

Recent investigations have shown that eosinophilia in COPD is a crucial indicator for people with asthma and other associated diseases, such as COPD [94]. Eosinophils are the blood cells that contribute to the modulation of inflammatory response, cell migration, the release of cellular mediators, antimicrobial activity, and allergic reactions [95]. Research suggests that elevated eosinophil is a biomarker for the response against COPD treatment [96]. However, the exact roles and functions of eosinophils remain largely unknown [97]. Additionally, the existence of eosinophilia in the peripheral blood or bronchi of COPD patients with challenging diseases is a sign that they should receive therapy. The significance of eosinophilia and the function of pro-eosinophilic mediators in the lungs have been highlighted by pharmacological advancements in the management of inflammatory conditions [98].

3.5. T-Lymphocytes

The T cell-mediated immune response in the lungs is associated with pathogen infection in COPD patients [99]. Increasing evidence suggests the role of T cells in the pathophysiology of COPD. As COPD advances, the development of lymphoid follicles is observed in airway linings [100]. Researchers found an increase in CD8+ and $CD4^+$ T cells in COPD [101]. Also, the T_H17 cell that produces IL-17 has been detected and linked with cigarette smoking-induced lymphoid neogenesis in COPD [102]. HIV-1 infection enhances T cell proliferation in COPD and increases the levels of $CD8^+$ T cells. In contrast, HIV-1-positive smokers had more CD8+ lymphocyte cells in endobronchial brushings than in BAL fluid. This was fueled by an accumulating sensory memory T cell population, a rise in tissue-resident recall T lymphocytes, and the mucosa of the airways [103].

Regulatory T cells (Tregs), characterized by the expression of CD4, CD25, and the transcription factor FoxP3, play a crucial role in maintaining immune homeostasis by suppressing excessive inflammatory responses and promoting immune tolerance [104]. In

the context of COPD, Treg dysfunction has been increasingly recognized as a contributing factor to chronic inflammation and the impaired resolution of immune responses. Studies have shown that both the number and functional capacity of Tregs are reduced in COPD patients, particularly in the lungs and peripheral blood [105]. This impairment compromises their ability to suppress pro-inflammatory T cell subsets such as Th1 and Th17, leading to persistent inflammation and progressive tissue damage. Additionally, the reduced Treg-mediated production of anti-inflammatory cytokines like IL-10 and TGF-β further diminishes their immunosuppressive function [106].

3.6. B-Lymphocytes

The role of innate immunity is well established; however, our understanding of the contribution of specific effector cells, especially T cells and B cells, is still in its infancy. Donovan et al. [107] investigated the role of T cells and B cells in the experimental model of COPD, and the study indicated that the T cell/B cell response is associated with extracellular remodeling (fibrosis/collagen deposition) and not inflammation. Kadushkin et al. [108] recently studied the B cell profile of smoking COPD individuals and suggested that higher levels of $CD27^-$ B cells as compared to $CD27^+$ variants caused there to be differential expression profiles of CCR7, CCR6, CXCR4, and CXCR receptors. This clearly showed the change in B cell phenotypes in COPD patients. Further research is necessary to explore the function of B cells at a molecular level in COPD [108]. Overall, the details of immune cells role in COPD are presented in Table 2.

Table 2. Immune cells and their functions in COPD.

Immune Cells	Function/Role	Effect	Molecular Signatures	References
Neutrophils (Section 3.1)	Protease-induced tissue damage	Acute exacerbations	IL-8 and CXC chemokines in COPD airways	[78,81]
Macrophages (Section 3.2)	Regulation of inflammation, tissue remodeling, and impaired phagocytosis	Sustained inflammation, emphysema, and impaired clearance of pathogens	TNF-α, IL-1β, IL-6, IL-8, ROS, MMPs (e.g., MMP-9), NF-κB, and STATs	[85–87]
Monocytes (Section 3.3)	Phagocytosis, cell migration, cytokine secretion, apoptosis, membrane vesicle shedding and differentiation	Alveolar epithelial cell death-driven lung tissue damage	Monocyte chemotactic protein-1.	[88,89,93]
Eosinophils (Section 3.4)	Inflammation, cell migration, release of cellular mediators, antimicrobial activity, and allergic reactions	Increase in alveolar space and a decrease in elastic rebound. Increase expression of age-related genes that regulates apoptosis, cytokine expression and antioxidant activity	Pro-eosinophilic mediators	[94,98]
T-lymphocytes (Section 3.5)	Pathogen infection in COPD patients	Development of lymphoid follicles	CD4+, CD8+, and IL-17	[100,102]
B-lymphocytes (Section 3.6)	Extracellular remodeling	Fibrosis/collagen deposition in lungs tissue	$CD27^+$ expressed differential profiles of CCR7, CCR6, CXCR4, and CXCR receptors	[108]

4. Inflammatory Mediators in COPD

Inflammatory mediators control the immune response and regulate the diverse functions of innate and adaptive immune response in COPD (Figure 3). In this section, the role of cytokines and related molecular mediators is discussed in the context of pulmonary inflammation in COPD. The role of inflammatory mediators as biomarkers of COPD has garnered significant attention due to their crucial involvement in the inflammatory processes underlying the disease [109,110]. Elevated levels of specific cytokines (e.g., TNF-α, IL-6, IL-8) in blood, sputum, and bronchoalveolar lavage fluid can indicate the presence and severity of COPD [72]. Higher inflammatory mediator levels often correlate with more severe disease. Changes in these levels can reflect disease progression. For instance, increasing levels of IL-6 and IL-8 might indicate worsening inflammation and declining lung function [73,109]. Elevated cytokine levels can predict acute exacerbations of COPD. For example, spikes in IL-6 and IL-1β levels can signal impending exacerbation, allowing for preemptive therapeutic interventions. Monitoring inflammatory levels may help to assess the efficacy of anti-inflammatory treatments in COPD [111,112]. This involves a few changes, including inflammatory mediators interacting in complex networks. Mediator levels can be influenced by numerous factors, including comorbidities, infections, and medications. Research is ongoing to better understand the role of cytokines in COPD and to develop reliable inflammatory-based biomarkers [111,113]. Advances in technologies such as multiplex assays and bioinformatics are improving our ability to analyze mediator profiles comprehensively. Using these mediators as biomarkers with other clinical and biological data could lead to more personalized and effective management of COPD [114–116].

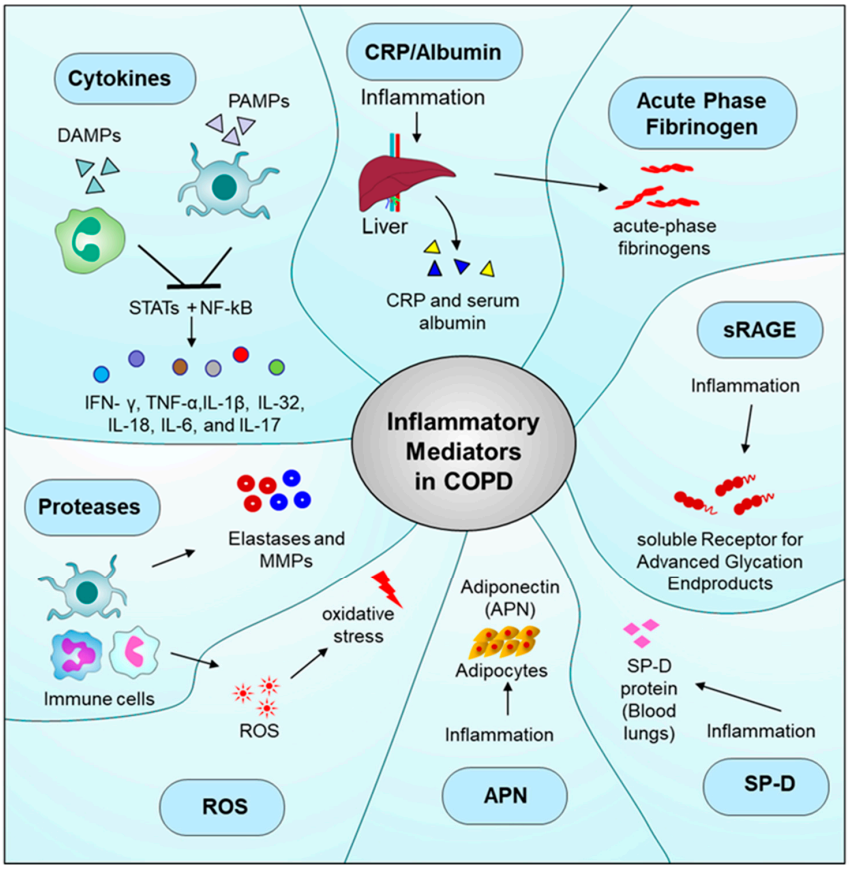


Figure 3. Role of inflammatory mediators in COPD: major inflammatory mediator and their role in COPD lungs.

4.1. Cytokines

Cytokines are small-cell signaling proteins that aid in the activation of immune cells during infection, tissue injury, and inflammation [117]. The increased expression of cytokines in serum, sputum, and lung tissue has been detected in COPD patients, suggesting their imperative role in pulmonary inflammation [19]. Toll-like receptors (TLRs) detect PAMPs (Pathogen-Associated Molecular Patterns) and DAMPs (Damage-Associated Molecular Patterns) and activate cellular signaling pathways to produce inflammatory mediators [118,119]. TLR signaling turns on a series of proteins inside the cell and further activates inflammatory pathways depending on their signal transducers and transcription activators (STATs) and nuclear factor kappa B (NF-kB) expression [120]. Reports showed that pro-inflammatory cytokines are essential in the pathogenesis of COPD [16]. The role of pro-inflammatory cytokines including interferon-γ (IFN- γ), tumor necrosis factor (TNF-α), and interleukins (IL-1β, IL-32, IL-18, IL-6, and IL-17) has been investigated in COPD [21]. T-helper (Th) cell subsets further shape this cytokine milieu. Th1 cells secrete interferon-gamma, affecting macrophage activation and cellular immunity, both of which are implicated in the pathogenesis of emphysematous changes [121]. Th2 cells, which produce IL-4, IL-5, and IL-13, are associated with eosinophilic inflammation and mucus hypersecretion features more prominent in COPD patients with overlapping asthma traits [122]. Notably, Th17 cells secrete IL-17, a cytokine that recruits neutrophils and contributes to steroid resistance, mucus production, and tissue destruction [123]. The relative predominance of these subsets influences the disease phenotype, severity, and therapeutic response, highlighting their critical roles in maintaining or disrupting immune homeostasis in the COPD lung microenvironment.

COPD progression is assessed by a complex interaction between pro-inflammatory and anti-inflammatory cytokines, resulting in a persistent inflammatory state that contributes to airway remodeling and lung tissue damage [124,125]. Pro-inflammatory cytokines such as interleukin-1β (IL-1β) and TNF-α are significantly elevated in COPD patients and are key drivers of neutrophilic inflammation, oxidative stress, and the recruitment of additional immune cells to the lungs [124]. In contrast, anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) function to suppress excessive immune responses and promote tissue repair [125]. However, in COPD, the production or activity of these anti-inflammatory cytokines is often impaired, leading to an imbalance that favors chronic inflammation.

Macrophages secrete TNF-α when there is inflammation in the lungs [126]. TNF-α causes tissue death and cell death. In COPD patients, the level of TNF-α was found to be significantly higher, demonstrating a solid link between TNF-α and COPD [127]. A meta-analysis of COPD patients and healthy individuals showed that the COPD group had much higher TNF-α levels [128]. Yao et al. [128] found that smoking cigarettes and getting older are two of the factors enhancing TNF-α-mediated inflammation. Along with TNF-α, the interleukin family proteins have also been linked with pulmonary inflammatory events in COPD. The IL-1 cytokine family regulates diverse functions, including immune responses against inflammation and tissue damage [129]. Research revealed that TNF-α and IL-1 are expressed differently in biomass COPD and tobacco smoke COPD [124]. Another study found an increased level of IL-1 compared to TNF-α, with severe airflow obstructions [124]. Lin et al. [130] found a link between COPD and pro-inflammatory cytokine (TNF-α and IL-1) levels in lung tissue from COPD patients. The levels were substantially higher in COPD patients and significantly reduced following lung protective therapy. This provided preliminary evidence with which to investigate TNF-α and IL-1 as potential biomarkers for inflammatory-induced lung damage in COPD patients. Feng et al. [131] used cigarette smoke (CS) and bacterial lipopolysaccharide (LPS)

to establish an animal model of COPD in control and TNF-α knock-out animals. Results showed that the inflammatory injury was significantly delayed by blocking the MAPK (mitogen-activated protein kinase) pathway and enhancing the activation of the suppressor of cytokine signaling-3 (SOCS3) and tumor necrosis factor receptor-associated factor-1 (TRAF1) in TNF-α knock-out animals [131]. MicroRNA molecules regulate pulmonary injury by regulating the inflammatory release in COPD and are responsible for the susceptibility, severity, and release of inflammatory cytokines. Recently, Wang et al. [132] showed that the microRNA-126 (miR-126) is associated with pro-inflammatory release and disease progression in COPD patients.

Anti-inflammatory therapy showed protection against COPD by decreasing the inflammation caused by cytokines. The lowered inflammatory markers (IL-8, TNF-α, and MDA levels) in a rat model of COPD after treatment with doxofylline resulted in less pulmonary inflammation and tissue stress [133]. Another study found that perilla leaf extract (PLE) had anti-inflammatory properties, lowering TNF-α, IL-6, and NO levels in a mouse model of COPD by targeting the TLR4/TLR4/NF-B pathway [134]. Researchers showed that COPD patients have high MRP8/14 (myeloid-related protein 8/14), IL-1β, and TNF-α levels in the serum and that these levels may serve as potential biomarkers [135].

4.2. C-Reactive Protein (CRP)

The levels of CRP and serum albumin may serve as useful biomarkers in the prediction of inflammation in COPD patients [136,137]. In COPD, the CRP/serum albumin ratio may be used in nutritional risk assessment [138]. A recent study showed an increase in the concentration of high-sensitivity CRP in patients with COPD, thereby suggesting its role as a potential biomarker [139]. A recent study showed that the use of montelukast sodium with ketotifen fumarate treatment reduced hs-CRP and Th17/Treg expression in COPD patients [140]. Montelukast is an anti-inflammatory compound that targets leukotriene receptors by blocking leukotriene D4. Ketotifen interferes with histamine release by targeting histamine (H1) receptors in the cells, suggesting that blocking CRP release with anti-inflammatory mediators may improve lung functions in COPD. In COPD patients above age 60, a significant relation is found between a rise in the expression of inflammatory markers, including Hs-CPR, and disease severity [141]. However, more in-depth analysis of this relationship is required to improve the management of COPD.

4.3. Fibrinogen

The idea of biomarkers has grown significantly in popularity, and the term is now frequently used to include blood or sputum tests, imaging modalities, and prediction algorithms [142]. The possible role of circulating inflammatory biomarkers in the progression of COPD has received some interest. Fibrinogen, a critical regulator of inflammation and fibrosis formation, as well as tissue damage, is one of the most well-researched inflammatory biomarkers [143]. Fibrinogen is a complex glycoprotein present in plasma that is predominantly synthesized in the liver and transformed into fibrin by thrombin-mediated proteolysis; inflammatory mediators upregulate the synthesis of acute-phase fibrinogens [142,144]. A new biomarker for COPD has emerged in the acute-phase plasma protein fibrinogen.

4.4. sRAGE

sRAGE (soluble Receptor for Advanced Glycation Endproducts) is a soluble, cleaved extracellular domain of RAGE (Receptor for Advanced Glycation Endproducts) [145]. According to reports, lower levels of sRAGE are linked with worsening pulmonary function in COPD patients [146]. In COPD, sRAGE interacts with extracellular fluid and removes

RAGE ligands from it [147]. The expression of sRAGE may serve as a protective mechanism as it prevents downstream inflammatory signaling.

4.5. CC16

The CC16 is named as such because it is expressed by Club/Clara cells in the lungs with a molecular weight of 16 kDa (CC16) [148]. CC16 is also known as uteroglobin, and it belongs to the globin family. It is effectively diffused into the bloodstream from the respiratory tract along a concentration gradient. CC16 exhibits anti-inflammatory properties and supports the homeostasis of the airway epithelium in the lungs when exposed to ozone, allergens, and viruses [148]. Although more prevalent in BAL fluid, CC16 can also be found in serum, urine, and sputum. Also, CC16 serum is used as a biomarker of epithelium integrity in the lung and permeability [149]. A lower-than-normal CC16 serum concentration is linked to more severe COPD and helps in diagnosis and evaluation [150].

4.6. Surfactant Protein D (SP-D)

One of the rare proteins found in the blood and lungs is known as SP-D [151]. SP-D is an important biomarker for COPD detection [152]. It maintains lipid hemostasis and the regulation of surfactants in the lungs. Low levels of BAL SP-D and high levels of SP-D are detected in COPD serum [152].

4.7. Adiponectin (APN)

APN is an adipocyte-produced secretory protein hormone that may perform a function in controlling the inflammatory response in COPD [153]. APNs may be utilized to help with risk assessment and therapeutic intervention by serving as a biomarker for the severity and development of the disease in COPD patients [45,154]. According to Lin et al. [155], in a meta-analysis, COPD patients had higher adiponectin levels than healthy controls.

4.8. ROS

Research suggests that ROS causes tissue injury and results in increased oxidative stress in the pathogenesis of COPD [156,157]. The primary immune cells, including macrophages, neutrophils, and epithelial cells, produce ROS in COPD patients [80]. To counterbalance oxidative damage, cells produce antioxidant mediators such as catalase, glutathione, and superoxide dismutase via the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway [158]. ROS regulates the inflammatory transcription pathways and the inhibition of sirtunin-1 (tissue repair mediator), and induces DNA damage [159]. The oxidative damage induced in COPD patients may also contribute to the aging of lung cells [160].

4.9. Proteases

Immune cells produce several proteases such as elastases and MMPs that contribute significantly towards the development of emphysema, neutrophil-mediated inflammation, and arterial stiffness in COPD [161]. In response to the damaging effects of proteases, lung cells produce α-1 antitrypsin as a key blocker of the protease activity [162]. The production of proteases is caused by the activation of cell receptors (toll-like receptors) by their cognate ligands, such as bacterial antigens (lipoproteins, LPS), which leads to the activation of intracellular signaling pathways that depend on NF-kB [163,164]. The protease–antiprotease imbalance is also a key mechanism driving alveolar destruction in COPD [165]. Elevated levels of proteases such as neutrophil elastase and MMPs, particularly MMP-9 and MMP-12, degrade extracellular matrix components like elastin and collagen, leading to the loss of alveolar structure [161]. Normally, α1-antitrypsin (A1AT) acts as a

major antiprotease to neutralize these enzymes. However, in COPD, chronic inflammation and oxidative stress impair A1AT function or expression, tipping the balance toward tissue damage [166]. This imbalance contributes significantly to emphysema and disease progression. Further, the genetic deficiency of A1AT, primarily due to mutations in the *SERPINA1* gene, is a well-established risk factor for early-onset COPD and other severe forms of the disease, particularly emphysema [167]. A1AT deficiency not only accelerates disease progression but also influences therapeutic response, as augmentation therapy with exogenous A1AT shows benefits primarily in individuals with severe deficiency. Early genetic screening and personalized treatment strategies are essential for managing COPD in patients with A1AT-related genetic susceptibility [166,167].

4.10. Antioxidant Defense Mechanisms

Oxidative stress plays a key role in the pathogenesis and progression of COPD, contributing to chronic inflammation, tissue damage, and impaired lung function [158,168]. Under normal physiological conditions, the lungs are equipped with robust antioxidant defense systems designed to neutralize ROS generated from both endogenous metabolic processes and exogenous sources such as cigarette smoke and environmental pollutants. Key components of this antioxidant defense include the Nrf2 pathway and the glutathione (GSH) system [169]. Nrf2 is a redox-sensitive transcription factor that regulates the expression of a wide array of antioxidant and cytoprotective genes, including heme oxygenase-1, superoxide dismutase, and glutamate-cysteine ligase [170–172]. Upon activation, Nrf2 translocates to the nucleus and binds to antioxidant response elements, promoting the transcription of genes that combat oxidative stress. The glutathione system, comprising reduced GSH and associated enzymes such as glutathione peroxidase and glutathione reductase, is another critical antioxidant mechanism [173]. GSH serves as a major intracellular antioxidant that detoxifies hydrogen peroxide and lipid peroxides. Studies have shown that GSH levels are depleted in the lungs of COPD patients, leading to a diminished capacity to neutralize ROS and exacerbating oxidative damage to airway epithelial cells, alveolar structures, and extracellular matrix components. The dysfunction of these antioxidant pathways contributes not only to direct oxidative injury but also to the amplification of inflammatory responses, cellular senescence, and impaired tissue repair mechanisms in COPD [173,174].

4.11. Categorization of Biomarkers in COPD

The biomarkers discussed can be categorized according to their diagnostic, prognostic, and therapeutic utility. Diagnostic biomarkers include CC16 and SP-D, which reflect epithelial damage and airway integrity [175] They also include sRAGE, whose decreased levels indicate emphysema and lung tissue destruction, and cytokines such as IL-1β and TNF-α, which are elevated in response to chronic pulmonary inflammation [147]. Prognostic biomarkers include CRP and fibrinogen, which correlate with disease severity, exacerbation risk, and mortality [176]. Adiponectin and certain microRNAs (e.g., miR-126) also show potential in predicting disease progression [177]. Therapeutic response biomarkers include IL-8, TNF-α, and CRP, whose levels decrease with effective anti-inflammatory interventions [178]. SP-D and CC16 may also reflect responses to therapy due to their roles in epithelial repair. Categorizing these biomarkers provides a framework for precision medicine in COPD, supporting early diagnosis, the monitoring of disease activity, and the assessment of treatment efficacy. Biomarker levels can be influenced by various factors, and their interpretation needs to be performed in the context of the individual patient and other clinical information. Research in this area is constantly evolving, and the clinical

application of many of these biomarkers is still under investigation. Overall, the details of selected inflammatory marker's role in COPD are presented in Table 3.

Table 3. Molecular inflammatory markers of COPD.

Inflammatory Markers	Activation Factor	Observations	References
Cytokines (Section 4.1)	Smoking cigarettes and aging	TNF-α-mediated inflammation	[128]
	Inflammation or tissue damage	IL-1 cytokine expression	[129]
	Cigarette smoke (CS) and bacterial lipopolysaccharide-induced inflammation	Activation of SOCS3 and TRAF1 signaling	[131]
	MicroRNA-126 (miR-126) release	Inflammatory cytokines release	[132]
C-reactive protein (CRP) and serum albumin (Section 4.2)	CRP/serum albumin ratio as potential biomarker	Inflammation-mediated CRP and albumin concentrations in the blood	[139]
Fibrinogen (Section 4.3)	Inflammation, fibrosis, and tissue injury	Upregulate the synthesis of acute-phase fibrinogens in the blood	[142,144]
sRAGE (Section 4.4)	Lower levels of sRAGE linked with exacerbating pulmonary function	Prevents the downstream inflammatory signaling	[146,147]
CC16 (Section 4.5)	CC16 exhibits anti-inflammatory properties	CC16 expression is induced by ozone, allergens, and viruses	[148,149]
Surfactant protein D (Section 4.6)	Lipid hemostasis and regulation of surfactants	High level of SP-D in serum	[151]
Adiponectin (Section 4.7)	Biomarker for the severity and development of COPD	High expression of APN	[155]
ROS (Section 4.8)	Tissue injury results in increased oxidative stress	Regulation of inflammatory transcription pathways, inhibition of sirtunin-1, and induces DNA damage	[158,159]
Proteases (Section 4.9)	Emphysema, neutrophil-mediated inflammation, and arterial stiffness	Elastases and MMPs expression in lungs	[161]

5. Conclusions

COPD will continue to be a global public health problem, with a largely unchanged risk factor. Demographic changes in high-income countries and an increase in non-communicable diseases in low-income countries will hasten the disease burden. However, individuals with COPD have a deterioration in their quality of life that is clinically substantial, including both general health conditions and prognosis. Another significant issue and challenge is the considerable variety of COPD symptoms. Finally, new care models for individuals with COPD and other chronic disorders must be devised. Considering the numerous comorbidities seen in COPD patients, there is a need for innovative forms of interdisciplinary treatment, therapeutic pathways, self-management, and rehabilitation.

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