

# Inflammatory and Immune Mechanisms in COPD: Current Status and Therapeutic Prospects

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**Background:** Chronic obstructive pulmonary disease (COPD) currently ranks among the top three causes of mortality worldwide, presenting as a prevalent and complex respiratory ailment. Ongoing research has underscored the pivotal role of immune function in the onset and progression of COPD. The immune response in COPD patients exhibits abnormalities, characterized by diminished anti-infection capacity due to immune senescence, heightened activation of neutrophils and macrophages, T cell infiltration, and aberrant B cell activity, collectively contributing to airway inflammation and lung injury in COPD.

**Objective:** This review aimed to explore the pivotal role of the immune system in COPD and its therapeutic potential.

**Methods:** We conducted a review of immunity and COPD published within the past decade in the Web of Science and PubMed databases, sorting through and summarizing relevant literature.

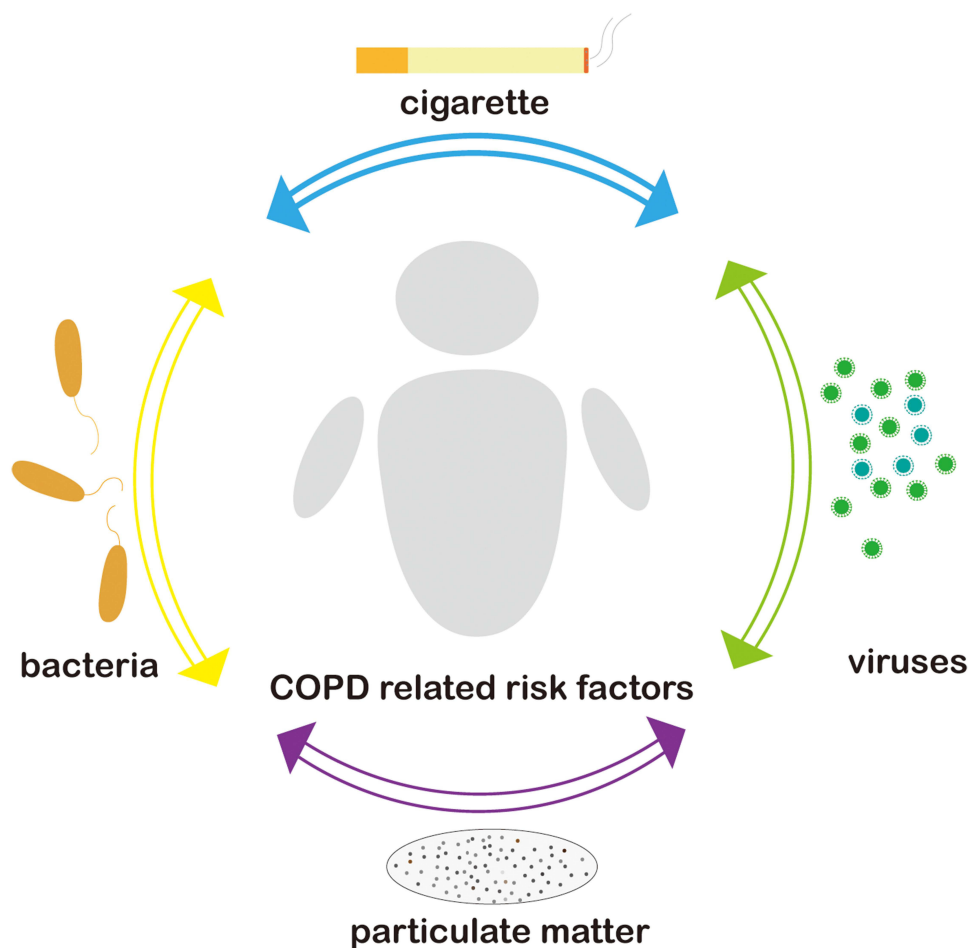
**Results:** This article examines the pivotal roles of the immune system in COPD. Understanding the specific functions and interactions of these immune cells could facilitate the development of novel therapeutic strategies and interventions aimed at controlling inflammation, enhancing immune function, and mitigating the impact of respiratory infections in COPD patients.

**Keywords:** COPD, immune system, inflammation, immune regulation

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) represents a diverse lung condition marked by persistent respiratory manifestations stemming from both airway and alveolar irregularities that result in sustained airflow limitation.<sup>1</sup> This prevalent global ailment disproportionately affects developing nations.<sup>2,3</sup> While early indications may be subtle, disease progression intensifies symptoms notably during physical exertion leading to substantial impairment in patient's quality of life.<sup>4</sup> Primary risk factors encompass tobacco smoke exposure (both active and passive smoking), environmental pollution (indoor and outdoor pollutants) as well as occupational hazards like dust or chemicals<sup>5,6</sup> (Figure 1). Prolonged tobacco use stands out as the foremost contributor to COPD with approximately 80–90% cases linked to smoking.<sup>7,8</sup> Typical signs comprise coughing fits accompanied by sputum production alongside dyspnea culminating in profound deterioration in overall well-being.<sup>9</sup>

The immune system serves as a vital biological defense mechanism that safeguards the human body against various pathogenic microorganisms.<sup>10</sup> However, in patients with COPD, abnormal activation of immune cells and the release of immune mediators can exacerbate lung inflammation.<sup>11</sup> Upon respiratory tract infection, the immune system promptly mobilizes to combat the invading pathogens.<sup>12</sup> Innate immunity effectively eliminates infections by engulfing viruses, bacteria, and other microorganisms while enhancing inflammatory responses to aid in their clearance,<sup>13–15</sup> adaptive immunity identifies, localizes, and eradicates specific pathogenic agents.<sup>16,17</sup> Prolonged exposure to harmful gases and particulate matter in COPD patients results in increased airway wall thickness, lung function impairment, and alterations in immune function.<sup>18,19</sup> Immune cells, particularly neutrophils and macrophages, often exist in a hyperactivated state



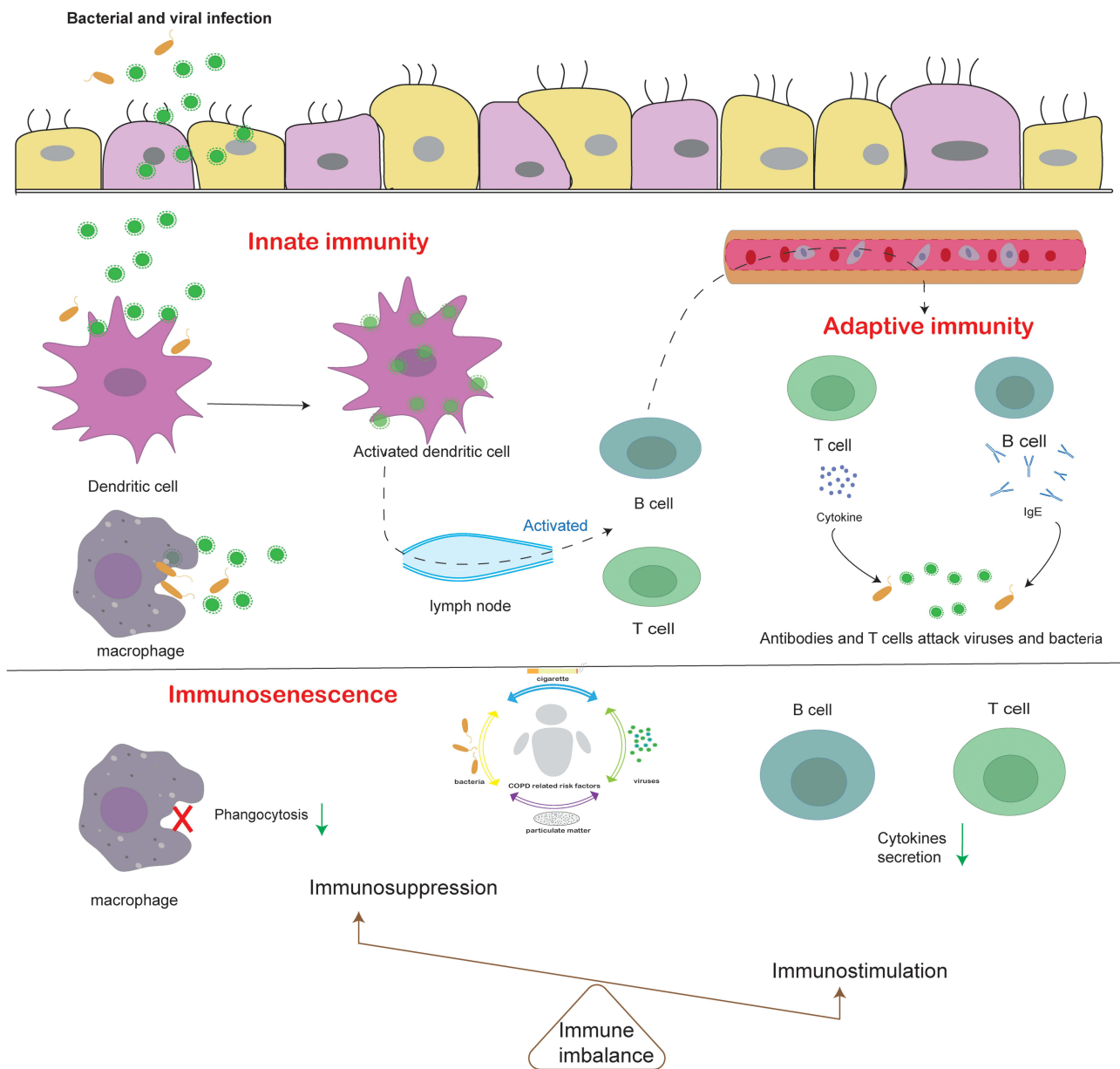
**Figure 1** COPD related risk factors. The risk factors include cigarette, bacteria, particulate matter and viruses.

producing elevated levels of inflammatory mediators which perpetuate an expanded inflammatory response.<sup>20,21</sup> Additionally, intricate interactions occur between immune cells and oxidative damage: oxidative stress can activate immune cells leading to the release of inflammatory mediators;<sup>22,23</sup> conversely, immune cells can generate oxygen free radicals and other oxidative substances contributing to further damage to lung tissue structure and function.<sup>24–26</sup>

Therefore, it is crucial to understand the role of the immune system in COPD prevention and treatment. This article begins by examining the significant role of the immune system in COPD progression. It then explored the relationship between COPD and immunity, offering new insights into potential directions for managing COPD.

## Immunosenescence in COPD

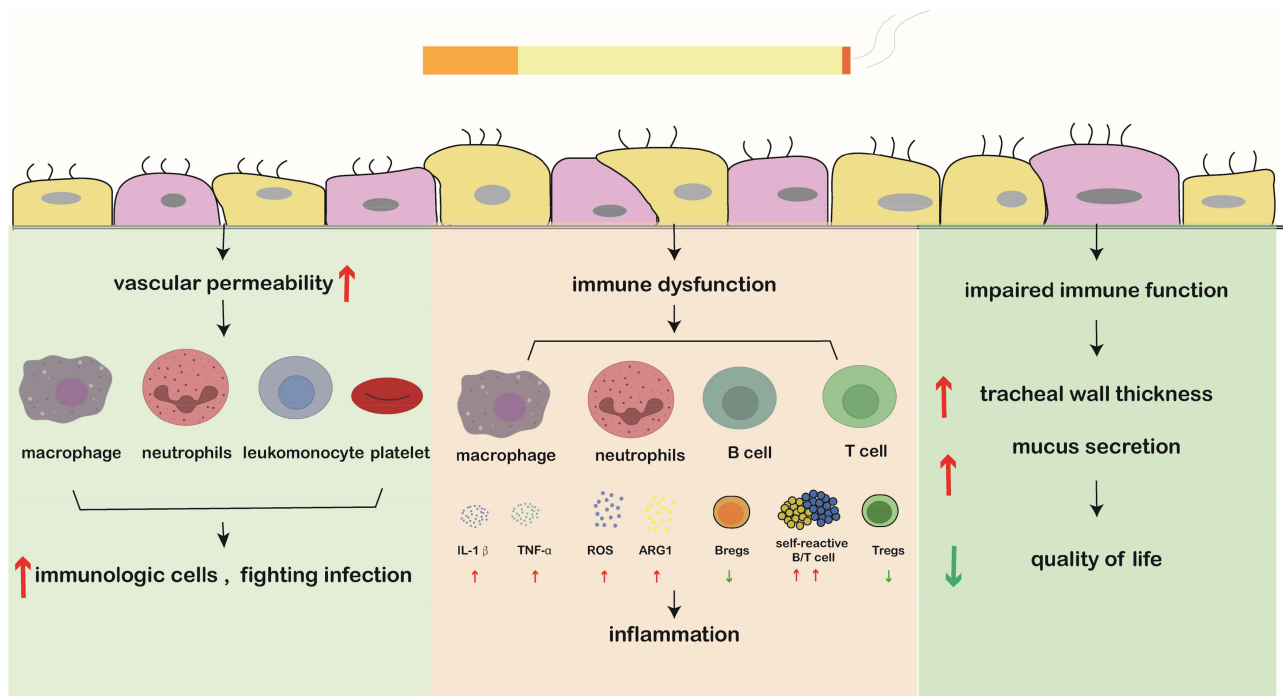
COPD is a chronic inflammatory disease, with environmental factors, such as smoking and air pollution, being the leading causes of chronic inflammation.<sup>27–29</sup> Chronic inflammation can damage the airway mucosal cells, increase mucus secretion, and impair respiratory function.<sup>30–32</sup> In response to this damage, the immune system initiates a series of responses to defend against aggressive factors.<sup>10,12</sup> Innate and adaptive immune responses build the body's immune defense system, protecting it from infection and disease.<sup>16</sup> However, immune aging exacerbates disease progression in patients with COPD.<sup>11</sup> During aging, the immune system may experience imbalanced regulation, leading to over-activation or suppression of the inflammatory response.<sup>33,34</sup> This imbalance can result in an attack on the lung tissue and exacerbate inflammation.<sup>35</sup> Overall, the immune response in COPD is a complex process that involves interactions between multiple immune cells and inflammatory mediators (Figure 2).



**Figure 2** Immune response in COPD. Innate and adaptive immune responses build the body's immune defense system. Immunosenescence exacerbates disease progression in patients with COPD.

## Inflammatory Response in the Lungs

When tobacco smoke, indoor and outdoor pollutants, dust, chemicals, etc., infiltrate the lungs or cause damage from various other irritants, the immune system triggers a cascade of inflammatory responses to counteract aggressive factors.<sup>36</sup> For instance, IL-33, IL-25, and TSLP are released in response to stimuli-induced epithelial cell damage.<sup>37,38</sup> ILC2s are innate immune cells that become activated and secrete proinflammatory type 2 cytokines such as IL-5 and IL-13 to recruit eosinophils and promote mucus production.<sup>39,40</sup> Meanwhile, T helper cells—adaptive immune cells—are activated by dendritic cells in an antigen-dependent manner. Inflammation is a crucial immune response to harmful substances and pathogens and plays a significant role in the immune response to COPD.<sup>41</sup> When pathogens or irritants enter the lungs and cause damage, the immune system initiates a series of inflammatory responses to defend against these aggressive factors.<sup>42</sup> For example, when lung tissue is irritated or infected, immune cells release various inflammatory mediators, these mediators guide the migration of other immune cells to the site of inflammation, regulate the



**Figure 3** The autoimmune mechanism of COPD. Cigarette smoke induces lung damage, leading to increased vascular permeability. This allows the infiltration of macrophages, neutrophils, lymphocytes, and platelets into the inflammatory site, triggering a series of defense measures by the immune system. However, immune dysregulation has been observed in COPD patients, including the release of IL-1 $\beta$  and increased TNF- $\alpha$  from macrophages, as well as ROS and increased ARG1 from neutrophils. Additionally, there is an increase in autoreactive T and B cells and a decrease in immunosuppressive regulatory T and B cells which exacerbate inflammation. Due to impaired immune function, patients with COPD experience airway wall thickening and more frequent mucus secretion that significantly impacts their quality of life.

inflammatory response, and increase vascular permeability and mucus secretion.<sup>43</sup> Increased vascular permeability allows plasma, platelets, and other immune cells to enter the site of inflammation, providing sufficient resources and immune cells to fight infection and repair damaged lung tissues.<sup>44</sup> Alveolar macrophages are an essential type of immune cell in the lungs that specialize in clearing pathogens and damaging substances.<sup>45,46</sup> They engulf and remove harmful substances during infection or injury, thereby releasing inflammatory mediators to activate other immune cells. The inflammatory response also plays a key role in triggering the repair and regeneration of the lung tissue.<sup>47–49</sup> After resolving inflammation, immune cells release various growth factors and cytokines to promote the regeneration and repair of lung cells, which helps restore function and structure within damaged lung tissue (Figure 3).

In summary, the complex process of the inflammatory response in the lungs fights infections associated with respiratory system injuries through coordinated actions, including the release of inflammatory mediators, dilation and leakage from blood vessels, and promotion of tissue repair for effective defense mechanisms within the lungs.

## Role of Innate Immunity and Adaptive Immune Responses

Upon exposure to external stimuli such as air pollution, harmful chemicals or infectious bacteria, COPD patients mount both innate and adaptive immune responses.<sup>50,51</sup> The term “innate” refers to this type of immunity’s universal presence within the body along with its immediate action.<sup>52</sup> Macrophages, natural killer cells, and phagocytes constitute key components of this defense mechanism against unfamiliar pathogens.<sup>53</sup> When confronted with external threats, intrinsic immunity rapidly identifies and eliminates pathogens while also initiating an inflammatory reaction that aids in tissue repair.<sup>54,55</sup> However, in individuals with COPD, this intrinsic immunity’s inflammatory response tends to be excessively activated. Exposure to hazardous substances triggers activation of macrophages, dendritic cells, and neutrophils within lung tissues, resulting in sustained inflammation, damage to airways.<sup>56,57</sup> Oxidative stress induced by smoking or air pollutants leads to heightened production of free radicals.<sup>58</sup> These free radicals not only directly harm lung tissue but also activate intrinsic immune cells, further exacerbating inflammatory responses.<sup>59</sup>

The adaptive immune system is distinguished by its high specificity, memory function, and is mediated by T cells, B cells, and other lymphocytes.<sup>60</sup> Upon initial exposure to a specific pathogen, the adaptive immune system generates corresponding antibodies, T-cells for combating said pathogen.<sup>61,62</sup> Moreover, it possesses memory capabilities, enabling faster, stronger responses upon subsequent encounters with identical pathogens. This attribute empowers our bodies' ability fight infections form immune memory.<sup>63</sup> In individuals suffering from COPD CD8<sup>+</sup> T cells CD4<sup>+</sup> T cell accumulate within lung tissues contributing towards airway inflammation. CD8<sup>+</sup> T cells cause direct damage to tissue through attacks on lung epithelial cells with CD4<sup>+</sup> T cell regulating inflammation via cytokine release.<sup>64,65</sup> B cell produced antibodies may be linked to airway inflammation among those afflicted with COPD. Although the main etiology of COPD is long term harmful exposure, abnormal antibody production may also aggravate inflammatory responses in some patients.<sup>66</sup>

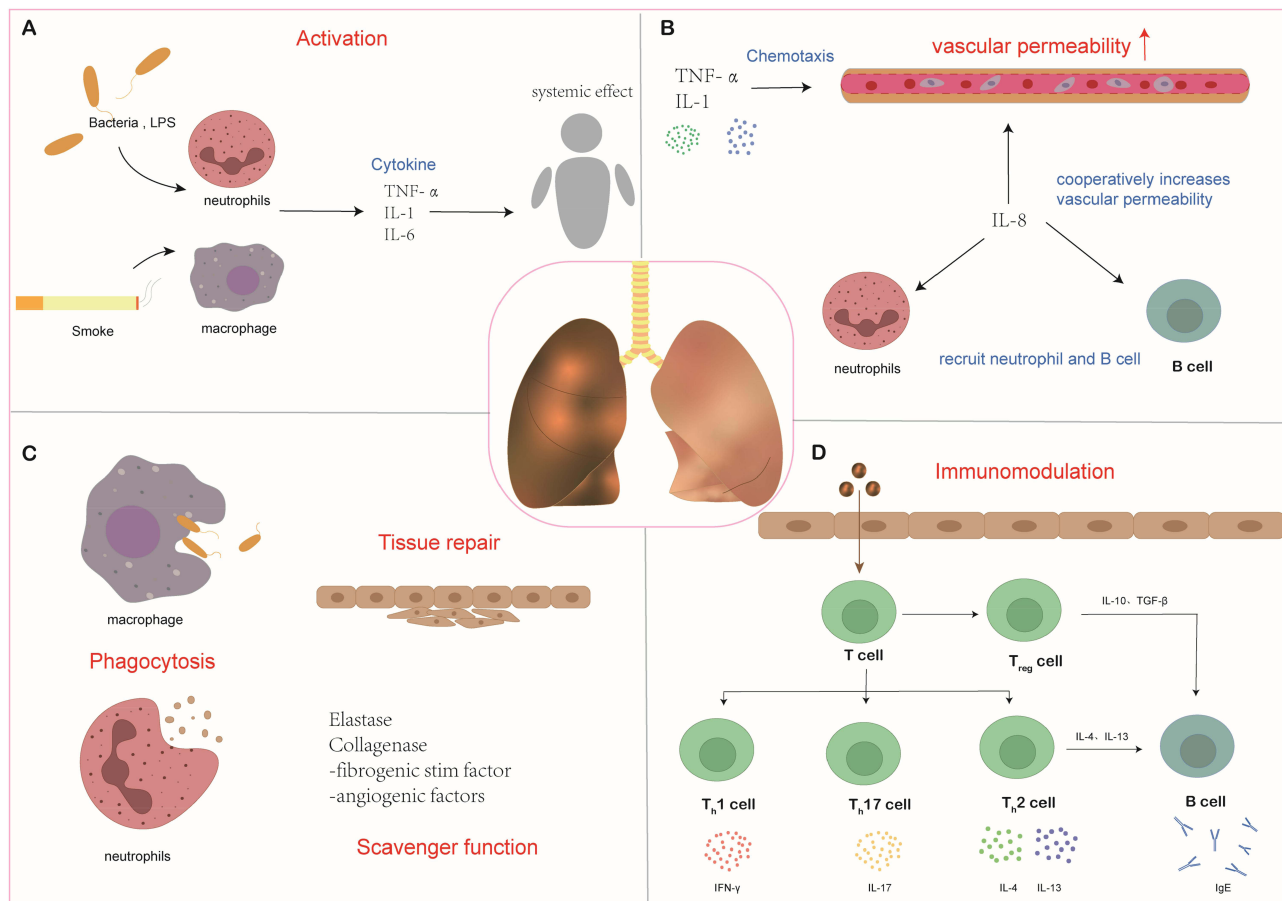
In summary, innate and adaptive immune responses collaborate to establish the body's immune defense system, safeguarding it from infection and disease. Their unique strengths and characteristics complement each other, harmoniously upholding the immune balance and homeostasis of the body. In academic research, a comprehensive understanding of the mechanisms of action of innate and adaptive immunity is crucial for disease prevention, control, and immune regulation.<sup>55,59,64</sup>

## Immune Aging in COPD Patients

Immunosenescence refers to age-related dysfunction of the immune system, which leads to decreased ability to combat infection and inflammation.<sup>63,67</sup> This process is particularly significant in patients with COPD, as studies have shown that the production and function of immune cells may be abnormally regulated, resulting in an overreaction to inflammation that exacerbates respiratory inflammation and airway obstruction.<sup>36,66</sup> With age, the function of immune cells, such as macrophages, T cells, and B cells, gradually declines in patients with COPD.<sup>68</sup> The activity and sensitivity of these immune cells decrease, resulting in a reduced ability to fight infections and clear pathogens, making patients more susceptible to diseases and inflammatory responses.<sup>69</sup> Immune aging also affects the memory function of immune cells in patients with COPD. Memory T and B cells of the adaptive immune system may be affected, thereby reducing the ability to recognize and respond to repeated infections.<sup>70</sup> This makes patients more susceptible to repeated infections by the same pathogen or exacerbates their condition. Furthermore, immune aging can lead to chronic inflammation in patients with COPD, a prominent feature that contributes to disease progression.<sup>71</sup> The slow inflammatory state induced by immune aging may exacerbate respiratory inflammation, oxidative stress, and airway remodeling. Given these implications for patient health outcomes, immunological intervention strategies targeting immune aging within this population have become increasingly important.<sup>72,73</sup> According to the characteristics associated with immune aging, some intervention measures can be taken, including improving activity levels among key immune cell types, promoting balance within regulatory mechanisms, strengthening vaccination protocols, and enhancing overall immunity through improved memory functions, all aimed at reducing inflammatory responses while controlling disease progression.<sup>74,75</sup>

## Role of Immune Cells and Mediators in COPD

In COPD, various immune cells and mediators are involved in the inflammatory responses and immune regulation.<sup>76</sup> The first were macrophages and neutrophils, which are among of the earliest immune cells involved in the inflammatory response.<sup>77</sup> Macrophages are among the initial immune cells that respond to inflammation. In COPD, irritants, such as smoking and air pollution, induce lung inflammation, activating macrophages to release inflammatory mediators, such as IL-1 $\beta$  and TNF- $\alpha$ , which subsequently trigger an inflammatory response.<sup>78,79</sup> Inflammatory mediators, such as elastase, released by neutrophils can lead to airway tissue destruction; the resulting reactive oxygen species (ROS) can further exacerbate oxidative stress and promote airway inflammation and damage.<sup>80</sup> Second, T lymphocytes play a crucial role in the immune response in COPD patients.<sup>81</sup> T cells consist of CD4<sup>+</sup> helper T cells and CD8<sup>+</sup> cytotoxic T cells, which regulate the inflammatory response and maintain immune balance by secreting cytokines and activating other immune cells.<sup>80,82,83</sup> Additionally, B lymphocytes contribute to COPD by producing antibodies that neutralize pathogens and antigens while participating in the fight against inflammation.<sup>84</sup> In addition to these immune cells and these inflammatory mediators, chemokines, leukocyte adhesion molecules, and humoral factors regulate and participate in inflammatory



**Figure 4** Role of immune cells and mediators in COPD. **(A)** Neutrophils and macrophages play crucial roles in immune responses. **(B)** TNF- $\alpha$  and IL-1 increase vascular permeability. IL-8 cooperatively increases vascular permeability and recruit neutrophils. **(C)** Neutrophils and macrophages phagocytose pathogens. Damaged tissue is removed by proteolytic enzymatic digestion. **(D)** Mechanisms of T cell and B cell.

responses.<sup>85</sup> In conclusion, complex interactions exist between immune cells and mediators in COPD pathogenesis, which regulate the inflammatory response and maintain the immune balance, thereby influencing disease development and progression<sup>86</sup> (Figure 4).

## Neutrophils and Macrophages

Neutrophils and macrophages play an important role in the development and inflammatory process of COPD.<sup>87,88</sup> Neutrophils release a large number of proinflammatory cytokines, such as interleukin-8 (IL-8) and TNF- $\alpha$ , which can recruit more inflammatory cells to the airway and further aggravate inflammation.<sup>89</sup> They secrete enzymes, such as elastase, collagenase and acid phosphatase, which can disrupt airway structure and function, leading to airway remodeling and tissue damage.<sup>90,91</sup> Neutrophils produce large amounts of reactive oxygen species, which can oxidize cells and tissues, leading to oxidative stress and inflammation.<sup>92</sup> ROS production is not only directly toxic to airway epithelial cells, but also aggravates airway inflammation.<sup>93,94</sup> Elastase and other proteases released by neutrophils break down components of the extracellular matrix (ECM), leading to destruction of airway walls and airway remodeling.<sup>95,96</sup> This tissue destruction is one of the important features of COPD.<sup>95,97</sup> Macrophages are normally responsible for engulfing and removing harmful substances from the body, such as bacteria, viruses, and inhaled particles.<sup>98</sup> In COPD patients, macrophages release large amounts of proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), and interleukin-8 (IL-8) in the airways of COPD patients due to long-term exposure to tobacco smoke and other harmful substances.<sup>99</sup> These factors are able to enhance the inflammatory response and recruit other inflammatory cells such as neutrophils to the airway, thereby exacerbating inflammation and tissue

damage.<sup>100</sup> Chemokines released by macrophages, such as CCL2 and CXCL8, promote the migration and accumulation of inflammatory cells, which lead to persistent inflammation and injury of the airways.<sup>101</sup> One of the major roles of macrophages in COPD is to maintain the chronic inflammatory state of the airways.<sup>102</sup> They maintain an inflammatory environment within the airways through the continuous release of inflammatory mediators and cytokines. It is more inclined to secrete proinflammatory cytokines and enzymes, which further aggravates airway inflammation and tissue damage. Macrophages secrete a variety of enzymes, such as elastase and metalloproteinase, which can decompose important components of the extracellular matrix (ECM), such as elastin and collagen.<sup>103,104</sup> This destructive effect leads to airway wall damage and remodeling, which further aggravates the condition of COPD.<sup>105</sup> Macrophages in COPD not only participate in the inflammatory response by secreting proinflammatory cytokines, but also may regulate the immune response by secreting anti-inflammatory factors such as IL-10 and transforming growth factor-beta (TGF- $\beta$ ).<sup>106</sup> However, this regulation may be out of balance in COPD, leading to persistent inflammatory responses.<sup>107</sup>

Although neutrophils and macrophages play an essential role in COPD development, an overactivated and dysregulated immune response can also cause inflammation and tissue damage. Therefore, it is essential to balance and control the activity of neutrophils and macrophages for treating COPD.<sup>108</sup>

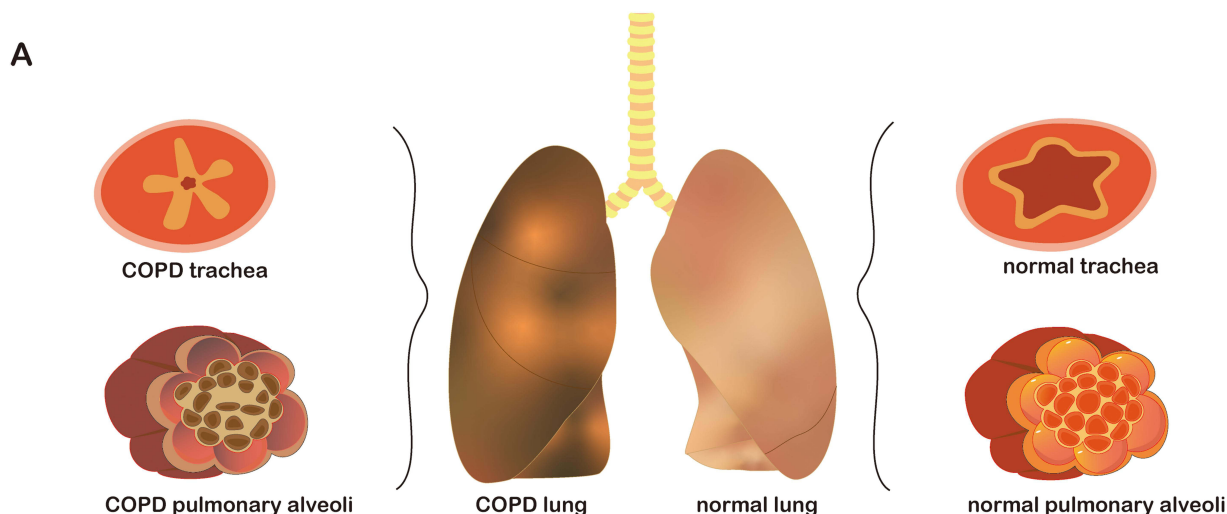
## T Cells and B Cells

T lymphocytes and B lymphocytes provide specific immune protection by recognizing and eliminating pathogens and other harmful substances.<sup>109,110</sup> These two types of adaptive immune cells are crucial for the immune response in COPD.<sup>111</sup> T cells, an essential part of the adaptive immune system, can be divided into CD4<sup>+</sup> helper T cells and CD8<sup>+</sup> helper T cells. They are involved in immune regulation and the regulation of inflammation in COPD.<sup>112</sup> The CD4<sup>+</sup> helper T cells can differentiate into different subpopulations, such as Th1, Th2, Th17, and regulatory T cells (Treg cells).<sup>113</sup> In COPD, there is an increase in the activity of Th1 and Th17 cells, leading to the production of cytokines, such as interferon-gamma (IFN- $\gamma$ ), from Th1 cells that stimulate inflammatory responses and cell damage.<sup>114</sup> Additionally, IL-17 produced by Th17 cells can lead to inflammation by stimulating the production of GM-CSF and CAM-1. Furthermore, Th2 cells contribute to excessive pathological remodeling of the respiratory tract, leading to airway obstruction, whereas the weakened function of Treg cells results in reduced immune tolerance and immune dysregulation.<sup>115</sup> B cells are another important component of the adaptive immune system that produces antibodies and participates in antibody-mediated immune responses. When activated, B cells differentiate into plasma cells that produce large quantities of clear pathogens.<sup>116</sup> In COPD, B cell activity increases, resulting in increased antibody production. Although antibodies play a role in pathogen clearance, it is essential to note that overactivated B cells may overproduce antibodies, leading to an autoimmune response.<sup>84</sup> B cells can also release cytokines and inflammatory mediators, further promoting the development of an inflammatory response.<sup>117</sup> In a chronic inflammatory state, such as COPD, the activity of B cells may increase, further stimulating the inflammatory response and oxidative stress.<sup>118</sup>

In COPD treatment, immunomodulatory strategies focusing on regulating the activity of T and B cells are anticipated to alleviate the inflammatory response and oxidative stress in COPD, thereby reducing symptoms and delaying disease progression.<sup>119</sup> Immunosuppressants, including those that inhibit T cell activity, can help reduce inflammatory lesions caused by immune response overactivation.<sup>120</sup> Regulating the Th1/Th2/Th17/Treg balance is expected to decrease inflammation in COPD.<sup>121</sup> Antibody drugs may also selectively interfere with B cell activity, reducing antibody production and the release of inflammatory mediators.<sup>122</sup> Collectively, T and B cells play important roles in the pathogenesis and inflammatory processes of COPD.<sup>123</sup> Therefore, immune regulation and antioxidant therapy may be crucial in COPD treatment.<sup>124</sup> Balancing the immune response, inhibiting the overactivation of inflammation, and alleviating oxidative stress are expected to improve symptoms and quality of life in patients with COPD while delaying disease progression.<sup>125,126</sup> This approach provides new ideas for personalized treatment in this field.<sup>127</sup>

## The Treatment Strategy for COPD

While current treatments for COPD effectively manage symptoms and slow disease progression, they possess inherent limitations.<sup>128</sup> In contrast, emerging immunotherapy presents distinct advantages by targeting specific inflammatory mediators or cells with precision to mitigate airway inflammation more effectively than conventional medications like



**B**

Therapeutic interventions that reduce COPD mortality				
Pharmacological therapy	Smoking cessation	PR	LTOT	NPPV

PR: Pulmonary rehabilitation  
 LOTO: Long term oxygen therapy  
 NPPV: Noninvasive positive pressure ventilation

**Figure 5** The treatment strategy for COPD. (A) The normal lung, trachea, and alveoli were compared with those of COPD patients. On the left are the lung, trachea, and alveoli of the COPD patient, while the normal tissues are shown on the right. (B) Therapeutic interventions that reduce COPD mortality.

bronchodilators or inhaled glucocorticoids which only alleviate symptoms without reversing or curing COPD entirely.<sup>129,130</sup> Furthermore, the variable efficacy of these medications among individuals underscores their limited impact on certain patients due to inadequate consideration of individual immune status and pathological features during treatment selection.<sup>131,132</sup> Immunotherapy holds promise in regulating immunity with greater specificity, potentially reducing both frequency and severity of acute exacerbations while enhancing overall quality of life through improved immune function in managing infections and injuries<sup>133</sup> (Figure 5).

### Current Treatment Options for COPD

According to the 2024 guidelines from the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), the management of chronic obstructive pulmonary disease (COPD) focuses on personalized treatment, symptom control, enhanced quality of life, and reduced acute exacerbations.<sup>134</sup> Smoking cessation stands as the foremost measure in COPD treatment.<sup>135</sup> Irrespective of the patient’s disease stage, smoking cessation is imperative for enhancing lung function, alleviating symptoms, and slowing disease progression.<sup>136</sup> Pulmonary rehabilitation encompasses tailored exercise training, education, and nutritional guidance to enhance exercise capacity, symptom management, and quality of life.<sup>137</sup> Long-term



**Table 1** Commonly Used Maintenance Medications in COPD

Type	Generic Drug Name
SABA	Fenoterol/Levalbuterol/Salbutamol
LABA	Arformoterol/Formoterol/Indacaterol
SAMA	Ipratropium bromide Oxotripium bromide
LAMA	Tiotropium/Umeclidinium
LABA+LAMA	Formoterol/aclidinium
LABA+ICS	Salmeterol/fluticasone propionate
LABA+LAMA+ICS	Fluticasone/umeclidinium/vilanterol
PDE-4 Inhibitors	Roflumilast

**Abbreviations:** SABA, short-acting beta<sub>2</sub>-agonist; LABA, long-acting beta<sub>2</sub>-agonist; SAMA, short-acting anti-muscarinic; LAMA, long-acting anti-muscarinic; ICS, inhaled corticosteroid; PDE-4, Phosphodiesterase-4.

oxygen therapy enhances both quality of life and survival in patients with persistent hypoxemia.<sup>138,139</sup> Pharmacotherapy is individualized based on symptom severity and risk of acute exacerbation<sup>140</sup> (Table 1). While long-term use of inhaled glucocorticoids can mitigate inflammation, it may also lead to side effects such as oral candidiasis, osteoporosis, and diabetes.<sup>141</sup> Prolonged use of certain medications may result in systemic side effects that could impact a patient's long-term health.<sup>142</sup> Despite medical therapy reducing exacerbation frequency overall; some patients with severe disease still experience frequent exacerbations leading to a significant decline in their quality of life.<sup>143,144</sup> Patients with COPD often have comorbidities (cardiovascular disease or diabetes) that may not be adequately managed by current treatment options.<sup>145</sup>

## Role of Immune Regulation in COPD Treatment

Immune regulation is crucial in treating COPD and can affect disease development and progression by controlling inflammatory responses, cellular immunity, and oxidative stress.<sup>146</sup> The chronic inflammatory response in COPD is central to its development. The over-activated inflammatory response destroys lung tissue, increases mucus secretion, worsens patient symptoms, and decreases lung function. Immune regulation can reduce the degree of inflammatory response by inhibiting the release of inflammatory mediators and regulating the activity of inflammatory cells, thereby improving lung symptoms and patients' quality of life.<sup>68</sup> T cells play a significant role in the immunopathological processes of COPD. Immune regulation can influence T-cell differentiation and function, increase Tregs, inhibit the activity of inflammatory T cells (Th1 and Th17 cells), balance cellular immune processes, and reduce the intensity of the inflammatory response.<sup>103</sup> Oxidative stress also plays a critical role in COPD pathogenesis and development by causing damage to the lung tissue through oxygen free radicals, which accelerate the decline in lung function.<sup>147</sup> Oxidative stress is a pivotal factor in COPD pathogenesis by inducing oxidative damage to lung tissue through oxygen free radicals which accelerates pulmonary function decline.<sup>108</sup> Immunoregulation has potential for mitigating oxidative stress progression while safeguarding against free radical-induced injury via antioxidant supplementation like vitamin C and vitamin E.<sup>26</sup> Tailoring immunomodulatory interventions based on individual immune status and disease characteristics is crucial for optimizing therapeutic outcomes in COPD management.<sup>70</sup> Immune monitoring and assessment enable selection of tailored immunomodulatory therapies that enhance efficacy while minimizing adverse effects.<sup>46</sup> Overall, immunomodulation significantly impacts COPD treatment by modulating inflammatory response, cellular immunity and oxidative stress thereby reducing disease burden while enhancing pulmonary function and quality-of-life whilst lowering acute exacerbation risks.<sup>148,149</sup>

## Summary and Discussion

COPD is a complex disease involving airway inflammation, airflow limitation and immune dysfunction.<sup>150</sup> Although current treatment methods include bronchodilators and anti-inflammatory drugs, there are still many patients who do not achieve satisfactory results. Therefore, immunotherapy for COPD patients has gradually attracted wide attention.<sup>7,151</sup> The application of immunotherapy in COPD has some potential advantages, which are different from traditional treatment methods and can provide new treatment options in specific clinical scenarios.<sup>152</sup> First of all, understanding the specific functions of immune cells and their roles in the inflammatory process can provide a basis for the selection of appropriate immunotherapy strategies. For example, inhibition of proinflammatory cytokines such as TNF- $\alpha$  and IL-6 may help to alleviate the inflammatory response of COPD.<sup>153</sup> The development of biological agents targeting specific immune cells or signaling pathways may become an important direction for the treatment of COPD in the future. Secondly, the immune status of COPD patients varies significantly, so individualized immunotherapy is particularly important. By assessing the patient's immune function, inflammatory markers, and disease severity, more precise treatment can be developed to improve the efficacy and reduce side effects. Immunotherapy can target specific biomarkers or signaling pathways that play a key role in inflammation and disease progression in COPD.<sup>154</sup> By precisely targeting these pathways, immunotherapy can reduce side effects and improve therapeutic efficacy. Finally, some immunotherapies, such as monoclonal antibody injections, can be administered in a clinic or home setting, which improves patient adherence to treatment. Traditional treatment of COPD often relies on inhalers, which may cause pharyngitis, oral microbial changes and other related side effects. Immunotherapy can reduce the dependence on these agents and the associated side effects.

The utilization of immunotherapy in the management of COPD holds significant promise, yet it also confronts numerous challenges.<sup>51</sup> Firstly, the chronic inflammation associated with COPD is not solely driven by immune cells but is also influenced by environmental factors (such as smoking and air pollution) and genetic factors.<sup>18</sup> Consequently, a singular immunotherapy approach may prove insufficient in addressing all inflammatory mechanisms. Secondly, the long-term efficacy and safety of immunotherapy necessitate validation through extensive clinical trials.<sup>155</sup> The majority of current studies have focused on short-term effects, leaving the long-term effects ambiguous.<sup>156</sup> Different types of immunotherapy may yield varying effects within distinct patient populations.<sup>51</sup> The accurate assessment and optimization of these diverse therapeutic effects remain an ongoing challenge.<sup>157</sup> Lastly, newer immunotherapies often entail higher costs, posing a financial burden for certain patient groups. Addressing this issue requires finding ways to reduce treatment costs while ensuring efficacy.<sup>158</sup>

In conclusion, the immune system plays a crucial role in the pathogenesis of COPD, and immunotherapy holds significant promise for its treatment. While current research is still exploratory, a comprehensive understanding of immune system function, personalized treatment strategies, and targeted immune pathway investigations are anticipated to offer new therapeutic prospects for COPD patients. Future research and clinical practice should prioritize addressing these challenges and integrating immunomodulation with drug therapy to enhance efficacy and improve patient quality of life. Advancements in this area will contribute to enhancing the quality of life for COPD patients and reducing disease burden.

## Data Sharing Statement

We confirm that the data supporting the findings of this study are available within the publicly available data, ensuring transparency and accessibility for further analysis and verification by interested parties.

The data that support the findings of this study are available at the following URL:

<https://www.ncbi.nlm.nih.gov/search/all/?term=COPD>

<https://webofscience.clarivate.cn/wos/woscc/basic-search>

Example from:

<https://pubmed.ncbi.nlm.nih.gov/36794439/>

<https://webofscience.clarivate.cn/wos/woscc/summary/abf1df08-5d61-444e-9bc8-2402f9adcaa2-e89680ff/relevance/1>.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by the National Natural Science Foundation of China (Grant/Award Numbers: 81973658, 82274339, 82104487); Bengbu Medical College Major Science and Technology Project Incubation Program (Grant/Award Numbers: 2020byfy001); Jiangsu Province Engineering Research Center for Cardiovascular and Cerebrovascular Disease and Cancer Prevention and Control (2022); University Natural Science Research Project of Anhui Province (Grant/Award Numbers: 2023AH051972); Jiangsu Higher Education Institution Innovative Research Team For Science and Technology (2023). Excellent scientific research and innovation team project of Anhui Province (Grant/Award Numbers: 2022AH010084).

## Disclosure

The authors declare no conflict of interest. The funders had no role in the design of the study, collection, analyses, or interpretation of data, writing of the manuscript, or in the decision to publish the manuscript.

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