Review

Innate Immunity

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Inherent immunity and adaptive immunity: Mechanism and role in AECOPD

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Abstract

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is the leading cause of hospitalization and mortality in COPD patients. The occurrence of antibiotic resistance and the progression of non-infectious diseases contribute to poor patient outcomes. Thus, a comprehensive understanding of the mechanisms underlying AECOPD is essential for effective prevention. It is widely acknowledged that the immune system plays a fundamental role in pathogen clearance and the development of inflammation. Immune dysregulation, either due to deficiency or hyperactivity, has been implicated in AECOPD pathogenesis. Therefore, the purpose of this review is to investigate the possible mechanisms underlying dysregulated immune function and disease progression in COPD patients, specifically focusing on the innate and adaptive immune responses. The ultimate aim is to provide new insights for clinical prevention and treatment strategies targeting AECOPD.

Keywords

AECOPD, COPD, immune system, complement, toll-like receptor

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Introduction

Chronic obstructive pulmonary disease (COPD) remains a significant global health challenge, ranking as the third leading cause of mortality.[1] Acute exacerbations of COPD represent the leading causes of hospitalization and mortality among these patients.[2,3] AECOPD, characterized by the rapid deterioration of airway function and respiratory symptoms, affect a substantial proportion of COPD patients. Annually, 22–40% of patients experience at least one exacerbation, while 9–16% suffer from multiple episodes.[4] The etiology of AECOPD is multifaceted, encompassing both infectious and non-infectious factors. Notably, bacterial infection accounts for approximately 50% of AECOPD cases.[5] Antibiotic therapy constitutes a cornerstone of conventional AECOPD management.[6–8] However, the therapeutic efficacy is often limited by the presence of non-infectious factors and antimicrobial resistance (AMR), resulting in suboptimal clinical outcomes and substantial economic burdens.[9] It is important to recognize that the pathogenesis of AECOPD, regardless of infectious or non-infectious etiology, is intricately linked to immune system dysregulation.[10,11] This review aims to provide a comprehensive analysis of the existing literature on the role of innate and adaptive immunity in COPD and AECOPD. By elucidating the mechanisms of action of infectious and non-infectious factors, this review provides novel insights into AECOPD management and evidence-based therapeutic strategies.

Innate immune response

The primary trigger of AECOPD is infection. Upon the initial entry of pathogens or foreign bodies into the internal environment, innate immune cells and molecules are activated, triggering the innate immune response. This innate immune response can be further categorized into two distinct stages: the humoral factor stage and the cell action stage, based on the type of effector products and the timing of their activity.[12] Subsequently, we will explore the specific mechanisms underlying the progression of COPD in the innate immune stage, focusing on two key aspects in detail.

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Action stage of humoral factors

In the early stage of humoral factors primarily depends on pre-existing and rapidly produced anti-pathogen effector components. This is exemplified by the activation and effect of the complement system. Complement is a complex network of proteins that is critical for both innate immunity and adaptive immune responses.[13] It facilitates the recognition and clearance of infected or damaged cells. Under normal physiological conditions, most complement components remain as zymogens, which can be sequentially activated by various activators, ultimately selecting their biological effects.

The activation of the complement system progresses through two stages: the early stage, also known as the front-end reaction, initiates a cascade that cleaves complement C3, producing C5 convertase; the late stage, also referred to as the terminal pathway, leads to the formation of the membrane attack complex (MAC) from C5 cleavage. This MAC produces a cytolytic effect, ultimately leading to the release of cell contents and promoting inflammatory reactions.

In terms of the diverse starting materials and activation sequences, the front-end reaction can be categorized into three distinct yet overlapping pathways, the mannan-binding lectin (MBL), classical, and alternative pathways. Notably, the MBL pathway emphasizes the role of the complement system in innate immune responses, whereas the classical pathway highlights its function in adaptive immunity. The alternative pathway, by contrast, primarily regulates the feedback mechanism of the complement system.[14]

Through clinical studies, it has been observed that the complement composition in COPD patients differs significantly from that of healthy individuals, and it undergoes corresponding modifications as the disease progresses. C1 is a macromolecular complex with a molecular weight of 750 kDa, consisting of a C1q molecule that non-covalently combines with two C1rs and two C1 s molecules. The spherical domains of C1q can bind to the Fc segment of IgG or IgM in immune complexes (ICs), leading to a conformational change in the six subunits of C1q. This conformational change results in the activation of C1r and its cleavage into two fragments, one of which exhibits enzyme activity.[15] Consequently, most studies on C1 proteins begin with an examination of C1q.

In COPD patients, the baseline serum C1q level is significantly lower than in non-COPD patients.[16] However, C1q possesses distinct protein-binding sites, with the head and handle regions of C1q containing two binding sites for Small Leucine-Rich Proteoglycan (SLRPS). Notably, only the head region can be activated by SLRP.[17] Moraxella catarrhalis, a respiratory pathogen, is a human-specific symbiotic bacterium that often triggers acute exacerbations in COPD patients. It is frequently found in mixed infections, with reports indicating that up to 50% of cultures may include bacteria such as Streptococcus pneumoniae or Haemophilus influenzae.[18,19] Evidence exists indicating that SLRPs can regulate complement activity, thereby enhancing its ability to kill Moraxella catarrhalis. This mechanism may reduce the likelihood of disease progression in COPD patients.[20] The researchers conducted a 56-month follow-up study on the bacterial pathogens isolated from sputum samples of 81 COPD patients. They found that Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, and Pseudomonas aeruginosa were long-term colonizers in the airways of COPD patients, which may contribute to the chronic inflammatory state observed in these individuals. Furthermore, the isolation of new strains of these bacteria was associated with a significantly higher risk of clinical deterioration in the patients.[21] Currently, researchers remain highly interested in the aforementioned bacteria. Notably, studies have found that the intracellular elongation factor thermo-unstable (EF-Tu) was exposed to the surface of NTHi (non-type able Haemophilus influenzae), and anti-NTHi EF-Tu IgG could promote the killing of NTHi and other non-encapsulated Gram-negative bacteria by the complement system, as well as the regulatory phagocytosis of Gram-positive bacteria.[22] In addition, Pseudomonas aeruginosa is strongly correlated with severe exacerbation of COPD patients and with a increased readmission rate of AECOPD patients.[23,24] However, there is currently no research showing that the complement system plays a significant role in the killing process of Pseudomonas aeruginosa. These findings underscore the critical role of C1q activation in the pathogen clearance of COPD patients, effectively preventing disease progression. Interestingly, an AECOPD patient experienced severe tongue edema due to angiotensin converting enzyme (ACE) inhibitors. Following the administration of C1 inhibitor, vascular edema was effectively treated.[25] This observation suggests a potential relationship between C1 overexpression and angioedema.

C3 is the most abundant complement protein in blood and a vital component of the complement system. It plays a crucial role in detecting and eliminating potential pathogens by interacting with other complement proteins.[26] C3 is primarily produced in the liver; however, immune cells and non-immune cells, such as lymphocytes, neutrophils, and mesenchymal cells, can also synthesize C3.[27,28] The central link of complement activation is the C3b molecule produced by C3 cleavage. Under normal circumstances, C3 molecules undergo spontaneous activation and degradation in the body, generating low levels of C3b fragments. When C3b deposits on the cell surface, it is rapidly inactivated by regulatory proteins. However, if C3b deposits on the surface of organisms lacking regulatory proteins, it cannot be inactivated. It then forms a complex with factor B called C3 convertase (C3bBb), leading to the activation

of more C3 to form C5 convertase (C3bnBb). This process culminates in the formation of the MAC due to the appearance of C5b, ultimately lysing target cells.[15]

It has been observed that individuals with lower C3 levels tend to have poorer outcomes in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD).[29] This finding aligns with previous research on C1, suggesting that insufficient levels of complement proteins may hinder the elimination of pathogenic organisms. It's interesting that the role of C3 in non-infectious inflammation appears to be intricately linked to the progression of AECOPD. It is well-established that the primary risk factor for AECOPD is exposure to cigarette smoke,[30] which triggers oxidative stress, a condition that can initiate chronic inflammation.[31] Oxidative stress activates the NF-κB pathway, particularly in airway epithelial cells (AECs) and macrophages, fueling inflammation. Additionally, TGF-β signaling pathway activation can exacerbate small airway fibrosis and oxidative stress.[32,33] Notably, C3 is stored within AECs and can protect these cells from stress-induced death.[34] Experimental data reveals that the C3 expression level is significantly up-regulated in AECs of mice and human COPD patients exposed to cigarette smoke extract (CSE) in vitro. Strikingly, C3 gene knockout in AECs enhances oxidative stress and apoptosis after CSE exposure, while exogenous C3 treatment mitigates CSE-induced AEC death in C3 knockout mice.[35] These findings underscore the protective role of C3 in COPD patients. Therefore, augmenting C3 levels holds promise for improving the prognosis of non-infectious COPD patients during exacerbations.

In addition to promoting oxidative stress and inflammatory reactions, cigarette smoke has also been identified as a complement activator.[36–38] Multiple studies have shown that cigarette smoke can increase the expression and functional reactivity of C5a receptors on human bronchial epithelial (HBE) cells. It can also enhance the expression of ICAM-1 and the adhesion of monocytes through C5a-mediated signaling. This mechanism is a key factor contributing to the chronic airway inflammation observed in COPD patients due to non-infectious factors.[39,40] Notably, the plasma C5a concentration is significantly higher in COPD patients compared to healthy smokers; however, no further significant systemic C5a increase is observed during acute exacerbations of COPD.[41] Subsequent research has found elevated levels of C3a and C5a in the sputum of both stable and exacerbated COPD patients.[41–44] Conversely, serum levels of C3a, C5a, and C4 decrease significantly during COPD exacerbations.[45,46] Researchers think that this may be due to the migration of locally activated complement components (including C3a and C5a) from circulation to lung tissue,[45] but there is still no substantial evidence. While the liver is the primary site of complement synthesis, lung epithelial cells and alveolar macrophages are capable of producing complement proteins.[47] C5a produced in lung tissue has been shown to activate macrophages in the presence of immune complexes, leading to the production of pro-inflammatory cytokines and chemokines.[48]

Cell action stage

Various cells in the human body express pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs), and scavenger receptors (SRs). Macrophages are the primary cells expressing these receptors. Upon pathogen invasion, macrophages recognize specific molecular patterns on the pathogen's surface through their surface and intracellular PRRs. This leads to the pathogen clearance, with the pathogen's characteristic antigens (such as protein fragments) subsequently presented on major histocompatibility complex (MHC) molecules on the macrophage surface. These antigens are then displayed to T cells, further activating the adaptive immune response.[49] One of the characteristics of COPD is the increase in alveolar macrophages in the lungs.[50] Theoretically, this increase in alveolar macrophages should enhance the pathogen clearance. However, several studies have shown that the response of alveolar macrophages in COPD patients is significantly impaired, with reduced phagocytic capacity for pathogens.[51,52] Researchers have found that, in response to stimulation with NTHI's lipooligosaccharide (LOS) and outer membrane protein P6, alveolar macrophages from COPD patients exhibit significantly reduced responses of IL-8, TNF-α, and IL-1β secretion. In contrast, there is no significant difference in the response of peripheral blood macrophages to NTHI antigens in COPD patients.[53] Similarly, alveolar macrophages from COPD patients show increased levels of Mcl-1, decreased apoptosis, and reduced bactericidal activity against serotype 14 Streptococcus pneumoniae, indicating impaired mitochondrial metabolism and bactericidal function, which leads to delayed bacterial clearance.[54] Further research has revealed a close connection between the diminished phagocytic ability of alveolar macrophages and the expression of TLR receptors on their surface. Studies have shown that alveolar macrophages from COPD donors prone to acute exacerbations exhibit resistance to IL-8 induction by pathogens such as NTHI, M. catarrhalis, and S. pneumoniae, which is linked to impaired TLR-2 and TLR-4 signaling pathways.[55] Upon ligand recognition, TLR2 or TLR4 undergoes conformational changes and recruits adapter proteins, primarily MyD88. Once activated, MyD88 recruits and activates IL-1 receptor-associated kinases (IRAKs), such as IRAK4 and IRAK1, which further interact with tumor necrosis factor receptor-associated factor 6 (TRAF6). The activation of TRAF6 initiates a signaling cascade that includes the activation of mitogen-activated protein kinase (MAPK) pathways and the IκB kinase (IKK) complex. Among these, the activation of IKKβ leads to the phosphorylation of IκBα (inhibitor of NF-κB). Phosphorylated IκBα is subsequently tagged for

Table 1. The expression and recognition characteristics of mammalian Toll-like receptors in innate immunity.

TLR	Expression site	Main ligand	Ligand source
TLR1	Membrane	Triacyl lipopeptide	Mycobacterium tuberculosis
TLR2	Membrane	Peptidoglycan, GPI anchor, lipoprotein, yeast mannan	Gram-positive bacteria, Trypanosoma cruzi, Mycobacterium tuberculosis, fungi
TLR3	Cytoplasm	Double-stranded RNA (dsRNA)	Virus
TLR4	Membrane	LPS, Lipoarabinomannan (LAM)	Gram-negative bacteria, Mycobacterium tuberculosis
TLR5	Membrane	Flagellin	Bacteria
TLR6	Membrane	Diacyl lipopeptide, yeast mannan	Mycobacterium tuberculosis, fungi
TLR7	Cytoplasm	Single-stranded RNA (ssRNA)	Virus
TLR8	Cytoplasm	Single-stranded RNA (ssRNA)	Virus
TLR9	Cytoplasm	Unmethylated CpG DNA	Bacteria, Herpes viruses
TLR10 (Human)	Unknown	Unknown	Unknown
TLR11 (Mouse)	Membrane	Profilin and related proteins	Toxoplasma gondii, urinary tract pathogens

degradation, thereby releasing NF-κB (primarily the p65/p50 dimer) from its inhibitory state. NF-κB then translocates to the nucleus, where it binds to specific DNA sequences and activates the transcription of various genes, which typically encode pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), immune modulators, and antigen-presenting molecules, ultimately contributing to the inflammatory response. Therefore, it can be concluded that the expression of TLR2/4 on alveolar macrophages (AMs) is closely linked to the exacerbation of COPD in patients. Additionally, animal studies have demonstrated that AMs differ from other macrophages in both their expression of TLR9 and their sensitivity to CpG oligodeoxynucleotides (CpG-ODN). Their low TLR9 expression is closely associated with reduced sensitivity to CpG-ODN, which has been shown to activate immune cells, highlighting the unique characteristics of AMs.[56] This finding also suggests a possible link between TLR expression and COPD progression. Interestingly, studies have shown that the innate immune response of AMs mediated by TLRs is impaired, potentially contributing to increased susceptibility to acute exacerbations in COPD patients.[55] Therefore, paying special attention to PRRs may provide important ideas and methods for the prevention and treatment of AECOPD.

Toll-like receptor. TLRs are essential protein molecules involved in nonspecific immunity, serving as a bridge between nonspecific and specific immunity. Discovered in the 1980s, the term "Toll" was coined by a German scholar while studying genes regulating the development of the dorsal ventral axis in Drosophila melanogaster. Subsequently, it was unexpectedly observed that the Toll gene also contributed to the formation of antibacterial barriers in Drosophila to prevent fungal infections.

In mammals, a transmembrane molecule family with a similar structure is involved in anti-infection, and its members include IL-1R and TLRs. Currently, 11 types of TLR have been identified in humans, each capable of recognizing distinct components and molecules of PAMP (Table 1). Many TLRs are associated with the progression of COPD. For instance, Pseudomonas aeruginosa flagellin stimulates TLR-5, leading to phosphorylation of p38, ERK, and JNK, which triggers the production of IL-6 and IL-8, thereby promoting COPD progression and exacerbation.[57]

Researchers infected lung whole tissue explants (WTEs) with viruses to investigate the impact of TLRs on COPD progression. The results indicated that TLRs 3, 7, and 8 activation in lung tissue stimulates the release of molecules like TNFα and CCL5, initiating pro-inflammatory responses.[58] Similarly, LPS activation of TLR4 leads to the release of IL-6, IL-8, and TNF-α, fueling inflammation and COPD progression.[59,60] Additionally, TLR4 overexpression in bronchial epithelial cells is observed with increasing COPD severity in patients, suggesting a close correlation between TLRs and COPD pathogenesis and exacerbation.[61]

At the cellular level, TLRs are expressed in various immune cells, including macrophages, dendritic cells, B cells, and certain T cells, as well as non-immune cells such as fibroblasts and epidermal cells. A characteristic feature of COPD is the increase in alveolar macrophages in the lung, whose role is to eliminate infectious agents.[50] Bacterial colonization in the lung is a common occurrence in COPD, and it promotes inflammation through persistent and repeated TLR stimulation. Interestingly, when the same bacteria are repeatedly stimulated, TLR tolerance is observed in COPD alveolar macrophages. However, upon repeated stimulation with different bacteria, TLR tolerance does not develop but rather leads to increased cytokine production.[62] As previously discussed, due to the diverse nature of bacteria in the lung, the same bacteria can stimulate different TLRs, resulting in repeated stimulation of numerous TLRs by various bacteria. This may represent a potential mechanism for excessive inflammation in COPD patients caused by bacteria.

As noted above, impaired immune responses such as macrophage tolerance play a significant role in AECOPD by hindering bacterial clearance from the lower respiratory tract.[63,64] Previous studies have shown that in COPD patients, AMs exhibit markedly dysregulated responses to TLR2 and TLR4 ligands of NTHI and impaired phagocytic function against NTHI.[52,53] Notably, this immune dysfunction extends beyond responses to NTHI alone.[65] To further investigate the mechanisms underlying impaired immune responses in COPD-associated AMs, researchers observed that healthy volunteers carrying heterozygous TLR4 SNPs showed a diminished systemic inflammatory response to inhaled LPS compared to wild-type controls,[66,67] suggesting a potential role for TLR polymorphisms in impaired immune function. In one study, DNA amplification of AMs from COPD smokers and controls revealed that, among COPD patients who had ceased smoking, AMs with the TLR9 (T1237C) SNP demonstrated reduced IL-8 responsiveness to NTHI, Mycoplasma catarrhalis, and Streptococcus pneumoniae, with no association found for TLR9 (T1486C). Furthermore, AMs carrying TLR9 (T1237C) but not TLR9 (T1486C) were correlated with reduced FEV_1% predicted values in these patients.[68]

These findings suggest that the intrinsic tolerance of TLRs to pathogens, as well as the impact of TLR polymorphisms on the tolerance of alveolar macrophages AMs to pathogens, could offer novel insights into controlling the inflammatory response in COPD patients.

In addition to its association with COPD progression induced by infectious factors, TLR also exhibits a certain degree of correlation in non-infectious inductions. As we are well aware, smoking is a major inducer. A study exposed alveolar macrophages from COPD patients and controls to CSE and then to TLR2, TLR4, and TLR5 ligands. The results showed that CSE exposure inhibited TLR-induced tumor necrosis factor TNF-α, IL-6, and IL-10 but did not affect IL-8 (CXCL8) production.[69] This suggests that smoking may lead to COPD progression by reducing macrophage killing capacity post-infection without affecting CXCL8 secretion. This, in turn, promotes neutrophil aggregation, leading to sustained local inflammation. Other studies have also examined the effects of smoking on TLR4, finding that smoking can induce differential expression of circulating miRNAs. For example, it can lead to miR-149–3p downregulation, which in turn regulates TLR4/NF-κB signaling to increase the inflammatory response in COPD patients.[70] Furthermore, smoking not only exasperates inflammatory symptoms by affecting macrophages but also increases the susceptibility of COPD patients to bacterial infections by interfering with the MyD88/IRAK signaling pathway and inhibiting Th1-mediated immune responses against Gram-negative bacteria.[71]

Compared to macrophages, TLR expression on other immune cells is relatively low in COPD patients. Nevertheless, TLR1, TLR2, TLR4, TLR6, and TLR2/1 expression on $CD8^+$ T cells is significantly increased in COPD patients compared to normal subjects. Moreover, activation of TLR2/1 receptors is positively associated with the severity of emphysema symptoms in patients. Additionally, activation of TLR2/1 receptors on $CD8^+$ T cells significantly enhances their ability to produce IFN-γ and TNF-α.[72] Furthermore, TLR expression on NK cells is also closely related to the progression of COPD. It has been found that stimulation of TLR3/7/9 expressing murine lung epithelial cells with TLR ligands and CS promotes surface expression of NKG2D ligands RAET1, leading to increased NK cell hyperactivity and airway dilation.[73] Therefore, TLR expression can also affect the inflammatory symptoms of COPD patients by influencing the function of T cells and NK cells.

Lectin receptor type C (CLR). CLR is a class of PRRs that bind to surface carbohydrates of microorganisms with the involvement of Ca^{2+}, expressed on macrophages, dendritic cells, and certain tissue cells. Some forms are soluble proteins found in the blood and extracellular fluids. The conserved carbohydrate recognition domain can recognize mannose, glucose, N-acetylglucosamine, and β-glucans.

In CLRs, research related to COPD has primarily focused on Dectin-1, langerin, CLEC5A, and Clec9A. Among these, Dectin-1 is an important immune receptor that recognizes β-glucan and plays a key role in antifungal immunity. In the respiratory system, Dectin-1 primarily mediates immune responses in lung epithelium against respiratory pathogens such as Aspergillus fumigatus and Mycobacterium tuberculosis. Immunohistochemical staining of lung tissue from 19 human subjects revealed that Dectin-1 was positive in 17 of the samples.[74] Furthermore, cell-based experiments have confirmed that Dectin-1 effectively recognizes Non-typeable Haemophilus influenzae (NTHI), a pathogen implicated in COPD progression, and triggers an immune response. However, there are currently no direct studies on the role of Dectin-1 in COPD exacerbation.

Langerin, another CLR, is expressed on a subset of dendritic cells (DCs) and plays a key role in pathogen capture and clearance through binding to carbohydrate ligands. Research has shown that langerin exhibits an unusual affinity for 6-sulfated galactose (Gal), a structure primarily found in keratan sulfate (KS). Interestingly, highly sulfated KS disaccharide L4 has been shown to inhibit lung inflammation, and it has demonstrated significant efficacy in a murine model of COPD and its exacerbation.[75] To explore the details and biological outcomes of this interaction, researchers synthesized and analyzed the corresponding chemical compounds, discovering that oligomerization of the L4 unit increased its affinity for langerin. However, it remains to be experimentally verified whether this L4 oligomer can directly reduce inflammation in patients with acute exacerbations of COPD.[76]

The type 1 conventional dendritic cell (cDC1 s) in DC cells expresses the C-type lectin domain family 9A (Clec9A), which plays a crucial role in cytotoxic $CD8^+$ T cell responses in cancer and viral infections.[77–79] To investigate the role of this type of CLR in the progression of COPD, a study detected the expression of Clec9A in both healthy controls and COPD patients. The results showed that compared to healthy individuals, serum Clec9A levels were elevated in patients with COPD at different stages. Furthermore, the percentage of $Clec9A^+$ DCs was increased in the bronchoalveolar lavage fluid of COPD patients compared to non-obstructive chronic bronchitis patients. Additionally, enhanced recruitment of $Clec9A^+$ DCs was positively associated with cytotoxic $CD8^+$ T cell responses in the bronchoalveolar lavage fluid of COPD patients. This study suggests that $Clec9A^+$ DCs participate in chronic airway inflammation mediated by $CD8^+$ T cells. It also indicates that CLR has a strong regulatory effect on the biological function of DC cells and that the over-expression of CLR in COPD patients is significantly associated with chronic airway inflammation in COPD patients.

C-type lectin receptor 5A (CLEC5A) is a PRR coupled with spleen tyrosine kinase (Syk), expressed on myeloid cells, and plays a role in innate immune responses to viral and bacterial infections. The impact of CLEC5A on acute exacerbations of COPD (AECOPD) is primarily mediated through macrophages. Studies have shown that CLEC5A is expressed on alveolar macrophages in mice exposed to cigarette smoke and in smokers. Furthermore, CLEC5A-mediated macrophage activation, without the use of LPS or GM-CSF, significantly increases cytokine production and promotes inflammation. Notably, COPD progression is driven by both infectious and non-infectious factors, and the presence of CLEC5A contributes to the exacerbation of inflammation in both contexts. Therefore, modulating the expression of CLEC5A on macrophages may offer a potential strategy to enhance the efficacy of COPD treatments.[80]

Other receptors with potential associations. Nucleotide-binding oligomerization domain-like receptors (NLRs) play a critical role in signaling transduction by recognizing PAMPs and damage-associated molecular patterns (DAMPs) in the cytoplasm. They are essential for the elimination of bacterial and viral pathogens. A clinical study examined the levels of NLRP3, its associated proteins, and cytokines in COPD and AECOPD patients. It was found that as the clinical symptoms of COPD patients exacerbated, the levels of NLRP3 protein and IL-8 increased. Suggesting that the activation of the NLRP3 inflammasome in both systemic and local airway tissues is associated with acute exacerbations of COPD.[81]

To investigate its specific mechanism of action, researchers demonstrated that by inhibiting NLRP3, the cytotoxicity and lung injury induced by PM2.5 combined with cigarette smoke, both in vitro and in vivo, occur through the activation of the NLRP3 inflammasome and pyroptosis pathway. This suggests that the NLRP3 inflammasome plays a critical role in airway inflammation induced by PM2.5-CS, a non-infectious factor.[82] Consequently, researchers have identified the regulation of the NLRP3 inflammasome as a potential therapeutic target for treating AECOPD. For example, it has been discovered that the lipid peroxidation product 4-hydroxynonena can directly disrupt the interaction between NEK7 and NLRP3, thereby inhibiting the NLRP3 inflammasome and preventing caspase-1 activation.[83] However, studies directly linking NLRs to AECOPD remain limited.

Moreover, scavenger receptors (SRs) are pivotal PRRs within the innate immune system.[84] However, research on the role of SRs in the pathogenesis and progression of COPD remains limited and predominantly observational. For instance, a genotyping study in at-risk smokers identified a strong association between the P275A mutation in the macrophage scavenger receptor-1 (MSR1) gene and increased COPD susceptibility, impaired lung function, and macrophage dysfunction.[85] Consistently, a large-scale Danish study reported that heterozygosity for the SRAI/II Arg293X mutation significantly impaired lung function in males and increased their risk of developing COPD.[86] These observational studies suggest a potential link between SRs and AECOPD, though robust experimental evidence is lacking.

While experimental studies remain limited, one study has offered valuable insights into the role of SRs in COPD progression. Specifically, alveolar macrophage SR-A has been shown to amplify inflammation induced by cigarette smoke extract, bacteria, and viruses, contributing to the persistence of COPD.[87] Although research in this area remains scarce, the dual role of SRs in mediating AECOPD caused by both infectious and non-infectious factors represents a promising avenue for further investigation.

Adaptive immunity

The adaptive immune response refers to the complete process in which antigen-specific T and B lymphocytes, upon receiving antigen stimulation, undergo self-activation, proliferation, and differentiation into effector cells, leading to a series of biological effects. Based on the different types of cells involved in the immune response and their mechanisms, the adaptive immune response can be categorized into two types: humoral immune response, which is mediated by B cells, and cellular immune response, which is mediated by T cells.

Cellular immunity

Mature T lymphocytes exhibit significant heterogeneity in terms of differences in cell surface molecule expression and biological functions. Based on the type of T-cell receptor (TCR), T lymphocytes can be divided into αβ T cells and

γδ T cells, with the former accounting for the majority and serving as the main effector cells mediating adaptive immune responses. αβ T cells can also be further classified based on their functional characteristics into helper T cells (Th), cytotoxic T lymphocytes (Tc), and regulatory T cells (Treg). Th cells primarily promote the activation and function of other cell types through cytokine secretion, exerting broad immunoregulatory effects. Tc cells have direct cytotoxic effects and play a crucial role in immune protection against viral infections. Treg cells are a type of cell named for their wide-ranging immunosuppressive/regulatory functions, which they perform in self-tolerance, peripheral tolerance, and inhibition of pathological immune damage. However, Treg cells in COPD will also have a negative side for patients. When Th cells are activated, they become effector T cells and secrete various lymphatic factor. These lymphatic factor play an important role in activating B cells, Tc cells, phagocytes and other cells involved in immune response. In COPD patients, Tregs, MDSCs, and exhausted PD-1(+) T cells contribute to the dysfunction of effector T cells.[88]

The exacerbation of COPD is usually triggered by respiratory pathogens such as viruses, which drive adaptive immune responses and expand the population of $CD8^+$ T cells in the lungs.[89] A clinical study found that compared to asymptomatic smokers with normal lung function, smokers with COPD had increased numbers of $CD8^+$ T lymphocytes and smooth muscle area in lung tissues, while the numbers of neutrophils, macrophages, and $CD4^+$ T lymphocytes were similar between the two groups.[90] Additionally, among COPD patients and smokers exposed to the same smoking factor, increased numbers of $CD8^+$ T cells were observed in the sputum of COPD patients.[91] This suggests a close association between disease exacerbation in COPD and the levels of $CD8^+$ T cells.

To investigate the relationship between $CD8^+$ T cells and COPD, researchers have used cell sorting techniques and found an increased abundance of two $CD8^+$ T cell subsets in mild-to-moderate COPD patients' lungs: cytotoxic $klrg1^+$ $TIGIT^+$ $cx3cr1^+$ TEMRA (T effector memory $CD45RA^+$) cells and DNAM-1^+ $CCR5^+$ tissue-resident memory (TRM) cells. These $CD8^+$ T cells interact with alveolar type II cells through IFN-γ and exhibit over-expanded TCR clone types, potentially leading to inflammation prior to severe disease.[92] Interestingly, these T cell subsets showed distinct spatial distribution patterns in the bodies of COPD patients, which may reveal their specific pathological features driving COPD, such as alveolar destruction and airway remodeling. TEMRA cells are primarily described as present in the blood and lymph nodes,[93] suggesting that their presence in the lungs may reflect transport through the pulmonary circulation rather than permanent residency. The observation of immune subsets in proximity to terminal bronchioles using imaging mass cytometry analysis further revealed their significant association with infiltrating $CD8^+$ T cells and their involvement in small airway remodeling. Selective $CD8^+$ T cells establish residence in the lungs following initial infection, exhibiting immune memory to encounter future challenges from the same pathogen.

This retention of immune cells in the terminal bronchus undoubtedly has a significant impact on the condition of COPD patients. We know that COPD is characterized by extensive infiltration of immune cells and alterations in tissue structure, such as bronchial fibrosis. Fibroblast-like white blood cells, known as fibrocytes, which are produced in the bone marrow and released into the peripheral circulation, are associated with lung fibrosis.[94,95] They can also be recruited in the blood of COPD patients during acute exacerbations.[96] Moreover, higher circulating fibrocyte counts during this stage are associated with an increased risk of mortality, indicating that fibrocytes may contribute to disease progression.[96] In addition to their roles in the generation of fibrotic extracellular matrix and impact on lung contraction function,[97] recruited fibrocytes may participate in pulmonary inflammation as antigen-presenting cells for T cells, thereby regulating fibroblast differentiation.[98]

Furthermore, researchers have found that fibroblasts and $CD8^+$ T cells are both located near the distal airways. Moreover, there is increased potential interaction between these two cell types in COPD patient tissues compared to the control group. The increased proximity and clustering of $CD8^+$ T cells and fibroblasts are associated with changes in lung function in patients. $CD8^+$ T cells from COPD patients promote fibroblast chemotaxis through the CXCL8-CXCR1/2 axis. In vivo imaging shows that $CD8^+$ T cells and fibroblasts establish short-term interactions, triggering $CD8^+$ T cell proliferation, pro-inflammatory cytokine production, $CD8^+$ T cell cytotoxicity against bronchial epithelial cells, and fibroblast immune regulatory properties, in a CD54 and CD86-dependent manner.[99] This provides another explanation for how infections can lead to exacerbation of COPD symptoms.

However, not all infectious pathogens in COPD patients lead to disease exacerbation. Research has found that there is a high expression of HHIP (a genetic variant associated with susceptibility to COPD) in lung tissues. Insufficiency in HHIP monomers induces the accumulation of T cells in the lungs.[100] Furthermore, fibroblast-specific depletion of HHIP enhances the accumulation of $IFN\gamma^+$ tissue-resident T cells after respiratory viral infection.[101] This suggests that genetic changes driven by common variations can alter the host's susceptibility to the retention of $CD8^+$ T cells. This also provides another explanation for why some clinical COPD patients develop AECOPD after an infection.

Smoking similarly affects the susceptibility of COPD patients to viral infections. Cigarette smoke exposure (CS) is recognized as a key cause of chronic pulmonary inflammation in the development and onset of COPD. Prolonged exposure to inhaled irritants can activate structural cells and

inflammatory cells in the respiratory tract.[102] Research has found that smoking impairs the immune response of COPD patients' $CD8^+$ T cells to viral infections. The smoke from cigarettes interferes with the production and presentation of MHC class I molecules, leading to impaired activation of $CD8^+$ T cells during viral infections.[103] Structural cells and inflammatory cells in the lungs react to CS exposure by releasing pro-inflammatory mediators, which recruit additional inflammatory immune cells to establish a chronic inflammatory microenvironment. Chronic inflammation leads to lung damage, impairs innate and adaptive immune responses, and promotes recurrent respiratory infections, thus exacerbating and further manifesting the pathological features of stable COPD.[104] In summary, regulating the function of immune cells, such as $CD8^+$ T cells, is a crucial direction for preventing AECOPD. Treg cells are a subgroup of $CD4^+$ T cells that express the transcription factor Forkhead box P3 (FoxP3) and are involved in maintaining self-tolerance to autologous antigens and eliminating autoimmune reactions.[105] The imbalance between inflammatory Th17 cells and regulatory Treg cells contributes to the progression of COPD. A clinical cross-sectional study revealed the immunophenotype of AECOPD patients, demonstrating abnormal activation of Th1, Th17, and Treg cells. The proportion of Th17 cells is correlated with the severity of COPD.[106] Similarly, in COPD subjects with rapidly declining lung function, the proportion of regulatory Tregs ($FoxP3^+/CD4^+$ CD25bright) is significantly lower than in subjects whose lung function did not decline rapidly.[107] Analysis of blood RNA sequencing data from COPD genetic epidemiological studies also suggests that COPD patients with lower $CD4^+$ T cell counts are more prone to AECOPD.[108] Given that Treg cells possess immunosuppressive functions, their low expression in COPD patients is likely an important factor in the occurrence and progression of AECOPD.

Smoking also impacts the function of Treg cells in COPD patients. Research has found that CSE exposure reduces the percentage of Tregs in $CD4^+CD25^+$ cells. Additionally, CSE intervention significantly upregulates IL-6 and TNF-α in HBE cells. Interestingly, COPD patient serum and CSE-exposed HBE cells secrete elevated levels of secreted Frizzled-related protein 2 (sFRP2). However, these findings are reversed following gene silencing of sFRP2.[109] Similarly, miR-29bs can regulate the imbalance between Th17 and Treg cells induced by CSE in experimental COPD by inhibiting the IL-22-dependent JAK/STAT3 pathway.[110] Such studies provide compelling evidence for the development of clinical interventions aimed at preventing and treating AECOPD.

Reports have shown that immune metabolism of Treg cells may play a role in the pathogenesis of COPD.[111,112] Glycolysis plays a central role in the induction and suppressive function of Treg cells in humans and mice, as the enzyme enolase-1 controls the expression of specific FoxP3 splice variants in human Treg cells.[113] Thus, studying the immune metabolism of Treg cells may provide new insights into the treatment of COPD patients. Furthermore, leptin, a powerful regulator of intracellular glucose metabolism and glycolysis, ranks first among circulating factors along with insulin and increases glucose uptake into cells. Plasma leptin levels are negatively correlated with lung function in COPD patients.[114–116] Therefore, determining whether leptin can intervene in COPD patients' lung function by regulating glycolysis and the function of FoxP3 splice variants in Treg cells offers hope for interventions in the clinical treatment of COPD.

Humoral immunity

B lymphocytes, also known as B cells, play a critical role in the immune system. They are derived from bone marrow and primarily reside in the lymphoid follicles of peripheral immune organs, constituting approximately 20% of the total peripheral lymphocytes. Upon antigen invasion, B cells can be activated, proliferate, and eventually differentiate into plasma cells, also known as antibody-producing cells (AFC). These plasma cells secrete specific soluble immunoglobulins (Ig), commonly referred to as antibodies. Antibodies mediate specific immune responses by binding to and clearing antigens, thereby exerting immunological effects. This immune response mediated by B cells is also known as humoral immune response.[117]

As an essential immune pathway, humoral immunity has a significant impact on the occurrence and development of diseases in patients. Similarly, in the context of COPD, an elevation of $CD4^+$ and $CD8^+$ T lymphocytes and B lymphocytes has been observed in both the large and peripheral airways.[118,119] As the severity of the disease worsens, the number of B cells and B cell-rich lymphoid follicles (LF) increases in the bronchioles of patients.[119–123]

Chemokines play a crucial role in LF formation. For instance, LF formation in the lungs of COPD patients can be achieved through the recruitment and/or retention of T and B lymphocytes expressing CXCR3.[124] Moreover, lung B cells can drive CXCL13-dependent mechanisms through TLR and lymphotoxin receptor signaling.[125] High expression of CXCL13 in lung tissues of COPD patients has also been confirmed.[126] B cells are the primary cellular population within these LF,[122] and their proliferation exhibits oligoclonal and antigen-specific characteristics.[123] The maturation, differentiation, and survival of B cells depend on B cell-activating factor (BAFF). BAFF is a type II transmembrane homotrimeric protein of the TNF family, expressed by innate immune cells, T cells, activated B cells, stromal cells, and airway epithelial cells.[127,128] It is widely present in immune cells within lymphoid follicles and the surrounding stromal cells.[129] Similarly, researchers have observed a significant increase in the expression of BAFF in the lungs of COPD patients and mice exposed to CS.[126,129] Further intervention studies involving prophylactic and therapeutic administration of BAFFR-Fc in

CS-exposed mice have shown a significant reduction in the number of B cells in lung tissue. This intervention also prevents CS-induced LF formation and the increase in immunoglobulin levels, significantly alleviating lung inflammation and preserving alveolar wall integrity.[129]

Inducible bronchus-associated lymphoid tissue (iBALT) has been found to play a crucial role in the occurrence of AECOPD.[121,129] iBALT possesses the ability to resist viral infections, thereby exhibiting pro-inflammatory effects.[130,131] However, they may have detrimental effects on the outcomes of chronic inflammatory conditions such as COPD.[132] Animal experiments have also demonstrated that the absence of iBALT can prevent CS-induced emphysema in COPD animal models.[126,133,134]

Currently, it is known that iBALT worsens the disease in AECOPD patients caused by infectious factors. To further explore the role of iBALT in AECOPD triggered by non-infectious factors, researchers have found that, especially during chronic CS exposure, oxysterols critically regulate iBALT formation and the immunopathogenesis of COPD. They have discovered that the expression of CH25H and CYP7B1 in airway epithelial cells is significantly upregulated, thus regulating CS-induced B cell migration and iBALT formation. This highlights the crucial role of cholesterol oxysterol metabolism in the localization of immune cells in secondary lymphoid tissues. Treatment with ketoconazole, an inhibitor of the oxysterol pathway, significantly inhibits iBALT formation and attenuates CS-induced emphysema, indicating that iBALT can be activated and formed under the influence of both infectious and certain non-infectious factors, leading to the exacerbation of COPD in patients. Therefore, this target may provide a new perspective for the clinical treatment of AECOPD.[135]

Antibodies, produced by the differentiation of B cells into plasma cells (effector B cells), are large Y-shaped proteins used by the immune system to identify and neutralize foreign substances such as bacteria and viruses. Based on their physical and biological properties, antibodies can be classified into five classes: IgM, IgG, IgA, IgE, and IgD. Among them, immunoglobulin A (IgA) is the primary first-line defense mechanism present on mucosal surfaces, including the airways. It is produced in the form of dimeric IgA (dIgA) and can (unlike monomeric IgA) bind to polymeric immunoglobulin receptor (pIgR) on epithelial cells, mediating their endocytosis into mucosal secretions. Studies have found that COPD is characterized by subepithelial deposition of IgA and related immune complexes, as well as increased expression of IgA and IgE in lung lymphoid follicles.[136–138] Particularly in AECOPD patients, there is a significant increase in the number of IgA^+ B cells in distal airway lymphoid follicles.[139]

Based on the characteristics of B cells, scientists have developed monoclonal antibodies, which are highly homogeneous and specifically target a particular antigenic epitope. These antibodies, derived from a single B cell with the ability to encode only one type of antibody, have been used in the treatment of various diseases. COPD is typically characterized by type 2 (T2) inflammation, in which Th cells release pro-inflammatory cytokines such as IL-4, IL-5, IL-9, and IL-13. This immune response may promote the production of IgE and increase/activate serum eosinophils. When COPD patients are exposed to certain environmental factors or non-infectious factors, this immune response can lead to excessive mucus production, airway inflammation, and other allergic reactions. In a clinical study that investigated the use of anti-IgE monoclonal antibody drugs in COPD patients, it was found that COPD patients with T2 inflammation showed significant improvement in lung function, X-ray sinusitis, and serum inflammatory markers after treatment with monoclonal antibody drugs.[140] In addition to monoclonal antibodies, researchers have also found that fluticasone propionate (FP) may reduce adaptive immune responses in COPD patients and may be more effective in patients with higher titers of autoantibodies/B cell/antibody responses.[141]

With the advancement of molecular biology research, two groups of opposing B cells have been defined based on the spectrum of cytokine production by B cells: effector B cells (Beffs) and regulatory B cells (Bregs). Beffs actively regulate immune responses by releasing pro-inflammatory cytokines such as interleukin IL-6, IFN-γ, and GM-CSF, while Bregs negatively regulate immune responses by releasing anti-inflammatory cytokines such as IL-10, IL-35, and transforming growth factor TGF-β.[142] Bregs act as a feedback mechanism to maintain immune balance by preventing excessive inflammation and tissue damage. Reduced and/or impaired Bregs have been observed in many autoimmune diseases, infectious diseases, and cancers, resulting in immune imbalance.[142–145] It has been suggested that Bregs may contribute to the pathogenesis of stable COPD (sCOPD).[146] Compared to never-smokers, the percentage of $IL\text{-}10^+$ Bregs in the circulating memory B cell subpopulation is significantly reduced in both flow-limited smokers and COPD patients without airflow limitation. This suggests that the decrease in Bregs and their impaired function may be associated with the occurrence and progression of AECOPD.[147] Further investigation into the specific mechanisms of action of Beffs and Bregs may provide important insights for the treatment of AECOPD.

Conclusion

This systematic review comprehensively summarizes the research on innate immunity and non-adaptive immunity, revealing the significant roles of both immune systems in the exacerbation of COPD. For instance, complement factors in innate immunity, as well as TLRs, NLRs, Treg cells, $CD8^+$ T cells, and fibroblasts in non-adaptive immunity, can profoundly impact the exacerbation and prognosis

of COPD patients. Moreover, this review deliberately analyzes and discusses the infectious and non-infectious triggers of AECOPD. For example, we found that the interaction between macrophage TLR expression and the microbiome may be an important underlying mechanism for infectious triggers of AECOPD. Additionally, the release of C3 complement components in AECs induced by smoking may offer significant avenues for preventing and managing non-infectious triggers of AECOPD. However, during the literature review process, we found that there is still insufficient innovation in experimental studies on AECOPD, which limits the exploration of new directions for clinical treatment and prevention. Therefore, this review primarily aims to provide new perspectives and directions for the clinical prevention and treatment of AECOPD by logically integrating existing literature-supported evidence.

Author contributions

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Yadan Tu: Methodology; Writing—original draft preparation;
Yong Chen: Formal Analysis; Writing—review and edition;
Chenghu Wang: Formal Analysis; Writing—review and edition; Visualization;
Yi Ren: Conceptualization; Software; Writing—review and edition;
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