What every clinician should know about inflammation in COPD

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The cellular nuances of inflammation in COPD can cause heterogeneous presentation and treatment response. The novel therapeutics detailed in this review could advance the field closer to precision medicine. https://bit.ly/4eeEvF0

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Abstract

Inflammation drives COPD pathogenesis and exacerbations. Although the conceptual framework and major players in the inflammatory milieu of COPD have been long established, the nuances of cellular interactions and the etiological differences that create heterogeneity in inflammatory profiles and treatment response continue to be revealed. This wealth of data and understanding is not only a boon to the researcher but also provides guidance to the clinician, moving the field closer to precision medicine. It is through this lens that this review seeks to describe the inflammatory processes at play in COPD, relating inflammation to pathological and functional changes, identifying patient-specific and disease-related factors that may influence clinical observations, and providing current insights on existing and emerging anti-inflammatory treatments and treatment targets, including biological therapies and phosphodiesterase (PDE) inhibitors.

Introduction

Chronic obstructive pulmonary disease (COPD), a collective term that includes chronic bronchitis and emphysema, has long carried the mantle as a leading cause of death and disability worldwide [1, 2]. Efforts at preventing disease development in the form of curbing modifiable risk factors, such as tobacco use and environmental exposures, coincide with a reduction in disease burden [3]; yet, in 2019, COPD was still the third leading cause of mortality globally, accounting for 6% of total deaths [4]. The Global Burden of Disease 2019 study reported 212.3 million prevalent cases of COPD across 204 countries and territories, with 3.3 million deaths and 74.4 million disability-adjusted life-years [3]. Although the overall age-adjusted point prevalence rates have decreased over the past 30 years, the absolute number of affected individuals has not [3]. In the United States, chronic lower respiratory disease is the fourth leading cause of death [5], and the median prevalence of COPD was 6.9% in 2022 [6], affecting almost 18 million adults.

The sequelae of COPD are driven by inflammation, which propels disease pathogenesis, influences outcomes and may contribute to comorbidity burden [7–10]. Understanding and targeting inflammation in COPD has been a complicated undertaking owing to the heterogeneous and dynamic nature of the disease. Where once it was believed that tobacco smoke exposure was the key precipitating event in the development of COPD, it is now known that approximately half of COPD cases worldwide have at least some of their origin in risk factors other than tobacco smoke exposure [11, 12]. Indeed, environmental exposures are an increasing concern due to short- and long-term air pollution, some of which are aggravated by climate change [13]. Whereas morbidity and mortality associated with COPD attributable to smoking, indoor air pollution, occupation exposures, secondhand smoke and lower ambient temperature have decreased globally over the past three decades, the burden of COPD related to climate change (*e.g.*, ambient particulate matter pollution, ozone and high temperature) has increased, particularly in regions with lower socioeconomic status [14].

A greater understanding of inflammation in COPD helps clinicians and researchers categorise patient phenotypes and endotypes (an important step toward precision medicine), assess treatment effects and

patient prognosis, and identify new treatment targets. During an era that has been marked by great pharmacological advancements across numerous disease states, there has been limited successful development of new treatment classes or refinements of offerings from existing drug classes for COPD, particularly treatments that target inflammation and immune dysfunction [15]. There is, however, continual development in this area, with promising investigational agents in the pipeline. In this narrative review, we will describe the inflammatory processes involved in COPD, identify factors that influence inflammation, and provide current insights on anti-inflammatory treatments and treatment targets.

Pathological and functional airway changes in COPD

COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as "a heterogeneous lung condition characterised by chronic respiratory symptoms (dyspnoea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction" [12]. The symptoms, pathological changes and functional impairment encompassed by this definition are the direct result of local (airway) and systemic responses to inflammatory triggers.

Exposure to cigarette smoke and other inhaled noxious particles has three major sequelae (the "pathogenic triad") that lead to the development of COPD: inflammation, protease–antiprotease imbalance and oxidative stress [7]. Airway and systemic inflammation will be described in greater detail in subsequent sections. Protease–antiprotease imbalance refers to an increase in proteases (*e.g.*, serine proteases, caspases and matrix metalloproteinases (MMPs)), which are secreted by damaged epithelial cells as well as by neutrophils, macrophages and airway smooth muscle cells, and a decrease in antiprotease activity due to the inhibition of endogenous antiproteases (*e.g.*, α_1-antitrypsin, secretory leukoprotease inhibitor and tissue inhibitors of MMPs) [7, 13, 16, 17]. In its most straightforward form, protease–antiprotease imbalance is typified by α_1-antitrypsin deficiency, wherein the activity of proteases, particularly neutrophil elastase, is unopposed due to an inherited lack of the antiprotease α_1-antitrypsin [7].

An increase in oxidative stress in the lung driven by chronic smoking or other environmental exposures, such as ozone or particulate matter, contributes to lung cellular damage, mucus hypersecretion, inactivation of antiproteases and inflammation [7, 13, 18, 19]. The recruitment and activation of inflammatory cells, such as neutrophils, in response to inflammatory signals generates reactive oxygen species, which in turn generate further inflammation [20]. Moreover, inactivation of proteases fosters the protease–antiprotease imbalance in the lungs of patients with COPD [18]. Oxidative stress is not limited to the lung; circulating neutrophils of patients with COPD have been shown to release more reactive oxygen species than those of healthy individuals, particularly during an acute COPD exacerbation [18, 21].

Accelerated or premature cellular senescence, the process during which cells age and no longer divide, is also believed to play a role in COPD pathogenesis [22–24]. Senescence in COPD may be a consequence of increased oxidative stress arising from exposures such as cigarette smoke, which has been shown to induce senescence in airway epithelial cells [22, 23]. Senescent cells undergo phenotypic changes resulting in the release of inflammatory cytokines, chemokines, proteases and growth factors, thereby generating low-grade inflammation that can spread beyond the lung [24].

Pathological changes

The pathogenic triad drives structural changes observed in COPD, including goblet cell hyperplasia, phenotypic changes to airway smooth muscle, mucus hypersecretion (chronic bronchitis), alveolar wall destruction (emphysema), and small airway inflammation and fibrosis (bronchiolitis) (figure 1) [7, 17, 25]. Changes in airway cell composition, including goblet cell hyperplasia, combined with release of inflammatory mediators such as neutrophil elastase, interleukin-13 (IL-13), IL-1β, IL-4, lipopolysaccharide, MMP-9 and others induce mucus hypersecretion, thereby contributing to airflow obstruction [26]. Individual patients may have a predominance of one pathology over another (*i.e.*, mainly emphysema *versus* mainly small airway disease), but most patients have a mix of pathologies [20]. The clinical presentation of COPD does not always reflect the particular underlying pathology due to the heterogeneity of the clinical COPD syndrome, imprecise definitions for airway pathology and the paucity of histopathological data in the clinical setting. There does appear to be a relationship between pathology and smoking status, with more small airway disease among nonsmokers with COPD and more emphysema among their smoking counterparts [27].

Functional consequences

The structural changes associated with COPD coupled with functional alterations, such as the epithelial barrier and mucociliary clearance dysfunction [13, 28], result in increased airway resistance and lung

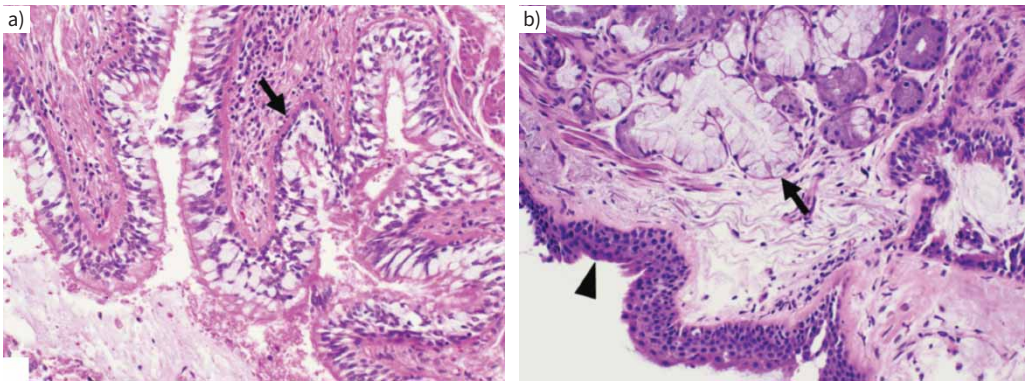

FIGURE 1 Histological features of chronic bronchitis. a) A section of bronchiole wall with luminal accumulation of mucus, goblet cell hyperplasia, basement membrane thickening (arrow) and scattered mononuclear inflammatory cells. b) A bronchial wall with squamous metaplasia of the luminal epithelium (arrowhead) and hyperplasia of the subepithelial seromucinous glands (arrow). Haemotoxylin-eosin, original magnification ×200. Reproduced with permission from Fischer *et al.* [7].

compliance, air trapping and progressive airflow obstruction [25]. From a clinical diagnosis standpoint, COPD is characterised by airflow limitation (*i.e.*, forced expiratory volume in 1 s (FEV_1) to forced vital capacity ratio <0.7 post-bronchodilation) that is not fully reversible [12]. A recent category of "pre-COPD" has been proposed to describe patients in whom respiratory symptoms, structural changes and/or functional abnormalities consistent with COPD are found, but for whom airflow obstruction is not detected during forced spirometry [12]. Individuals with pre-COPD are at increased risk for developing airflow obstruction over time, although not everyone with pre-COPD develops COPD. It is likely that genetic predisposition influences specific pathways or patterns of inflammation that may be involved in the transition to COPD but more research is needed in this area.

Airway inflammation in COPD

Airway inflammation in COPD is dynamic and dependent on both the innate and adaptive immune responses and interactions with a variety of environmental stimuli. The inflammatory processes in COPD are characterised by the recruitment of neutrophils, macrophages, lymphocytes and, for some patients, eosinophils (table 1) [8, 9, 16, 18, 27, 29–47]. Neutrophils are the most consistently elevated of these immune cell types, with increased levels observed in airways, bronchoalveolar lavage fluid (BALF), sputum, lung tissue and blood samples of patients with COPD. The degree of elevation in the various cell types is influenced by factors such as disease severity, smoking status, lung function, health status, phenotype and prognosis. For example, clinical data indicate that neutrophil levels in sputum from smoking patients with COPD are higher than those of nonsmokers with COPD [27]. A higher blood neutrophil count has also been associated with a worse prognosis in COPD, including risk for exacerbations, hospitalisations and mortality [8, 9]. Although an increase in eosinophils is observed in only a subset of patients with COPD, elevated blood or sputum eosinophil counts may portend a response to treatment with inhaled corticosteroids in the prevention of exacerbations [45, 46] or systemic corticosteroids for the treatment of exacerbations [47].

Neutrophils

Neutrophils are leukocytes that, along with monocytes, basophils and eosinophils, develop from a common myeloid progenitor. Neutrophils are a key component of the innate immune system, accounting for 50% to 70% of circulating leukocytes in humans and participating in the acute phase response to an array of pathogens [48].

Neutrophilic inflammation in the airway is induced by multiple triggers, including smoke or other particulate matter exposure, bacterial or viral infection, and oxidative stress, which initiate a complex and interwoven cascade of cellular events and signalling pathways (figure 2) [13, 17, 18, 20]. Response of the respiratory tract epithelium to these stimuli results in the release of inflammatory exosomes, cytokines and chemokines (*e.g.*, IL-6, IL-8, leukotriene B4 (LTB4) and tumour necrosis factor-α (TNF-α)), which recruit inflammatory cells, including neutrophils, to the site of injury [18, 49, 50]. IL-8, also known as CXCL8 (C-X-C motif chemokine ligand 8), is the primary cytokine involved in the chemotaxis of neutrophils and

TABLE 1 Inflammatory cell types implicated in the pathogenesis of COPD

Cell type	Changes observed in COPD	Associated with	Responds to [18, 29–31]	Produces/releases [16, 29, 30, 32]
Neutrophils [9, 33–35]	↑ (airways) ↑ (BALF) ↑ (sputum) ↑ (lung) ↑ (blood)	Disease severity [9, 33, 34, 42], smoking status [27], lung function [43], health status [43], prognosis [8, 9]	IL-6, IL-8, LTB4, TNF-α, CXCL1, CXCL2, CXCL5, CXCL7, RANTES	IL-1, IL-8, NE, MMP-1, MMP-9, MMP-12, MPO, NETs, HMGB1
Macrophages [34, 36]	↑ (airways) ↑ (BALF) ↑ (lung) ↑ (sputum)	Disease severity [34]	MCP-1, MIP-1α, RANTES	IL-1β, TNF-α, IL-8, IL-23, MCP-1, ROS, MMP2, MMP-9, MMP-12, CXCL1, CXCL2, CXCL5, CXCL9, CXCL10, CXCL11, CXCL16, MIP-1α, eotaxin-1, CCL15, CCL18, CCL20
Lymphocytes [34, 37–40]				
$CD8^+$ (Tc1)	↑ (sputum) ↑ (lung) ↑ (blood)	Disease severity [34], smoking status [44], lung function [34]	CXCL9, CXCL10, CXCL11	IFN-γ, TNF-α, granzyme B, perforins
$CD4^+$ (Th1, Th17)	↑ (lung) ↑ (blood)	Disease severity [34]	IL-6, IL-1β, IL-23, CXCL9, CXCL10, CXCL11	IL-2, IFN-γ, TNF-α, IL-17A, IL-17F, IL-21, IL-22, IL-23
Eosinophils [41]	↔ or ↑ sputum[#] blood[#]	Disease severity [41], phenotype [42], ICS response [45, 46], SCS response [47]	IL-5, GM-CSF, RANTES, CCL7, CCL11, CCL13, CCL15, CCL24, CCL26, CRTH2, PGD_2	MBP, ECP, EPX, EDN, IL-2, IL-3, IL-4, IL-5, IL-10, IL-12, IL-13, IL-16, IL-25, RANTES, CCL11, CCL13, TNF-α, TGF-β

BALF: bronchoalveolar lavage fluid; IL: interleukin; LTB4: leukotriene B4; TNF-α: tumour necrosis factor-α; CCL: CC ligand; CXCL: C-X-C motif chemokine ligand; NE: neutrophil elastase; MMP: matrix metalloproteinase; MPO: myeloperoxidase; NETs: neutrophil extracellular traps; HMGB1: high-mobility group box 1; MCP-1: monocyte chemoattractant protein-1; MIP-1α: macrophage inflammatory protein-1α; ROS: reactive oxygen species; IFN-γ: interferon-γ; GM-CSF: granulocyte–macrophage colony-stimulating factor; PGD_2: prostaglandin D2; MBP: major basic protein; ECP: eosinophilic cationic protein; EPX: eosinophil peroxidase; EDN: eosinophil-derived neurotoxin; TGF-β: transforming growth factor β; SCS: systemic corticosteroids. [#]: elevated counts are observed in a subset of patients with COPD.

is produced by multiple cell types, including epithelial cells, endothelial cells, macrophages and airway smooth muscle cells [51, 52]. IL-6 activates neutrophils, promoting tissue infiltration and triggering the release of enzymes and proteases – including neutrophil elastase, MMPs and myeloperoxidase – that are involved in the destruction of the elastic matrix of alveoli [16, 18, 51]. Moreover, enzymes and peptides produced by activated neutrophils cleave elastin fibres and collagen, fragments of which promote further neutrophil and monocyte recruitment, thus propagating the cycle of inflammation [7, 51, 53–55]. Neutrophils from patients with COPD have been shown to contain proteolytic enzyme concentrations as much as 25 times greater than those of healthy individuals [54].

Macrophages

Macrophages play several important roles in the lungs, including inflammation resolution (*e.g.*, clearing inflammatory cells and proteases), cellular debris removal, immune surveillance and phagocytosis of pathogens, and processing foreign matter such as cigarette smoke and particulate matter [36, 56]. Notably, although the number of macrophages in patients with COPD is elevated, the macrophages themselves are functionally compromised [57]. Defects in phagocytosis render alveolar macrophages incapable of clearing respiratory pathogens and debris, thus disrupting the lung microbiome [57–60].

In the context of COPD, macrophages respond to chemokines and cytokines produced by the airway epithelium that has been exposed to pathogens or irritants (figure 2) as well as to chemokines (monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α)) produced by

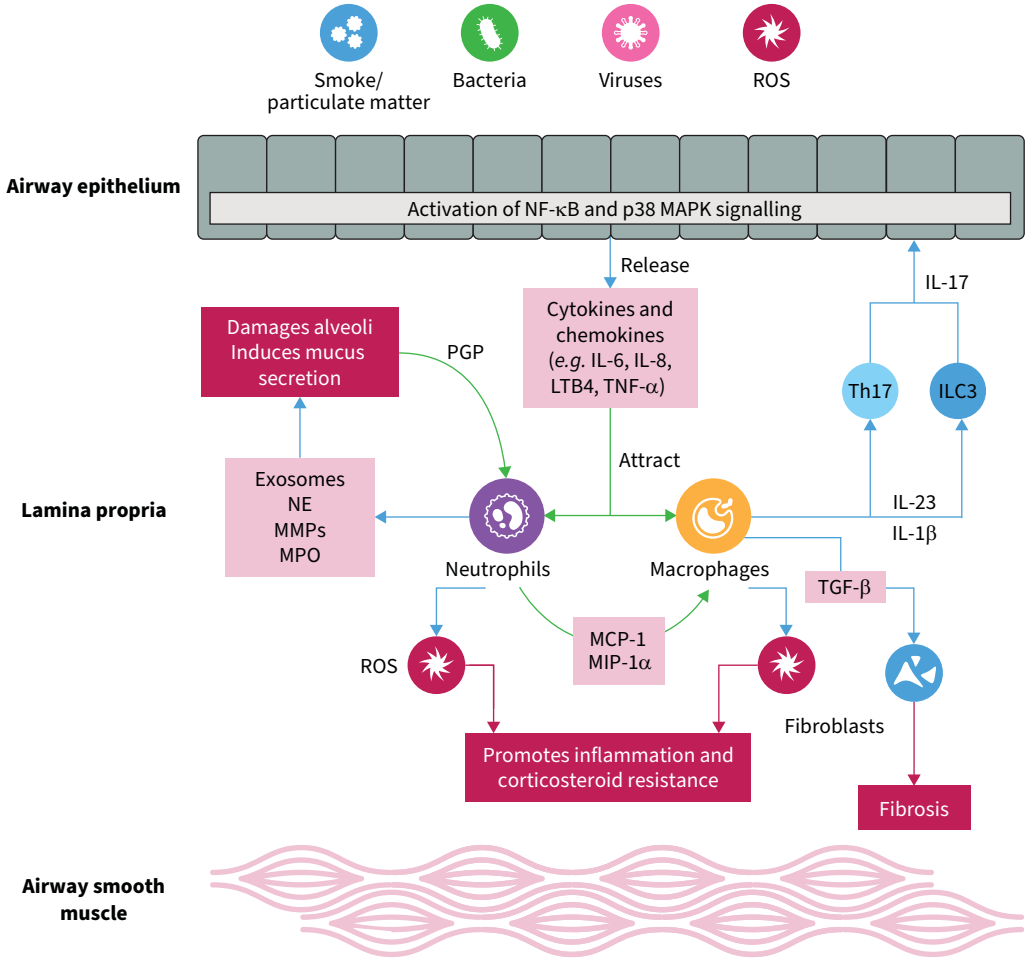

FIGURE 2 Pathways involved in neutrophilic airway inflammation in COPD [17, 18, 20]. Airway epithelium exposed to inflammatory triggers release cytokines and chemokines that attract neutrophils and macrophages. These cells, in turn, release proteases, reactive oxygen species (ROS) and proinflammatory mediators that propagate inflammation and contribute to airway remodelling, tissue damage and mucus hypersecretion. IL: interleukin; ILC3: type 3 innate lymphoid cells; LTB4: leukotriene B4; MAPK: mitogen-activated protein kinase; MCP-1: monocyte chemoattractant protein-1; MIP-1α: macrophage inflammatory protein-1α; MMPs: matrix metalloproteinases; MPO: myeloperoxidase; NE: neutrophil elastase; NF-κB: nuclear factor kappa B; PGP: proline–glycine–proline; TGF-β: transforming growth factor-β; TNF-α: tumour necrosis factor-α.

neutrophils [18]. Macrophages, particularly those that have been activated to a proinflammatory phenotype, are a source of numerous inflammatory mediators, including IL-1β, IL-6, IL-8, IL-23, LTB4, TNF-α, transforming growth factor-β (TGF-β), reactive oxygen species, MCP-1 and MMPs [16, 20, 36, 61, 62]. These inflammatory mediators further propagate inflammation and promote the differentiation and activation of myofibroblasts, major contributors to the development of fibrosis [51, 56]. Macrophages originating as bone marrow-derived monocytes can transition to myofibroblasts (a process known as macrophage–myofibroblast transition), which further contributes to the development of fibrosis [56]. Macrophages are also a key producer of MMPs in COPD, which have been implicated in alveolar destruction [51, 63].

Lymphocytes

Whereas neutrophils and macrophages are part of the innate immune response, lymphocytes are involved in the adaptive immune response that contributes to COPD pathogenesis. Lymphocyte airway infiltration in COPD includes T-cell subtypes ($CD4^+$, $CD8^+$) and B-cells [34, 64]. By contrast, regulatory T-cell numbers in the airways of patients with COPD may be decreased or comparable to those of healthy individuals [40]. Lung tissue damage related to the actions of T-cells is the result of direct action in the form of T-cell-induced cytotoxicity and indirect action through the activation of macrophages and B-cells [64].

Of the T-cell types, $CD8^+$ cells are more abundant and more strongly implicated in the pathogenesis of COPD compared with $CD4^+$ cells [37, 38]. This is the opposite of the pattern observed in asthma, wherein $CD4^+$ cells are the predominant cell type [65]. $CD8^+$ cells exert their effects through three actions: secreting cytokines (*e.g.*, interferon-γ (IFN-γ) and TNF-α), generating and releasing cytotoxic granules (*e.g.*, granzymes, perforins) and inducing apoptosis in target cells [66]. Among the $CD4^+$ T-cell types, Th1, Th2 and Th17 are associated with COPD [31]. These cells secrete a variety of interleukins, including IL-17A, IL-17F and IL-23, as well as IFN-γ and TNF-α. Th17 cells produce proinflammatory cytokines that signal to epithelial cells, causing them to produce inflammatory molecules that perpetuate inflammation [31]. B-cell number has been shown to correlate with disease severity [34], but the role of B-cells in COPD pathogenesis is not known [66].

Eosinophils

Eosinophils, which arise from a common myeloid precursor along with monocytes and neutrophils, are typically associated with conditions that have a type 2 inflammation component, such as asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps and eosinophilic oesophagitis [67, 68]. The reason for elevated eosinophil levels occurring in only a subset of patients with COPD is unknown but is likely due to a mix of genetic and environmental factors [20]. It has been observed that sputum eosinophil counts are higher in patients with COPD who have comorbid allergy or asthma (past or present) than those with COPD alone [20, 41, 69]. Although eosinophil counts may also be elevated in plasma samples from patients with COPD, eosinophil counts in sputum and blood are not well correlated and provide different phenotypic and prognostic information [41]. Interestingly, longitudinal studies have shown that elevations in eosinophil counts are not persistent for the majority of patients with COPD [70, 71].

Heterogeneity of inflammation in COPD

The presence of inflammatory cell types and inflammatory markers measured in blood, sputum or tissue samples varies within patients over time due to external factors, such as infection and exacerbation, and may differ between patients due to the influence of inherited conditions or other etiological factors and comorbidities. The relationship between dysbiosis and inflammation is also of interest and forms the basis of some pathophysiological hypotheses in COPD. Local and/or systemic inflammation may also be augmented by lifestyle factors such as smoking/smoke exposure, poor nutritional status, low levels of physical activity and obesity [72, 73]. Epigenetic alterations are likely to be involved in the sequelae of inflammation in COPD and can modulate treatment effects and the natural course of the disease.

Exacerbations

Exacerbations are frequently elicited by respiratory viral infections, although bacterial infection, air pollution, ambient temperature or other triggers of inflammation may also precipitate or worsen COPD exacerbations [74–76]. The inflammatory nature of exacerbations is reflected in the current GOLD definition, which describes an exacerbation as “often associated with increased local and systemic inflammation caused by infection, pollution, or other insult to the airways” [12]. The immune response during an exacerbation is heterogeneous and is driven by the underlying pathogen [47]. Viral infection increases inflammatory mediators (*e.g.*, IL-6, IL-8, RANTES, TNF-α and CXCL10), thus promoting the recruitment of immune cells [76]. This response is amplified in patients with COPD compared with healthy individuals [76, 77]. Moreover, patients with COPD who have frequent exacerbations may be more susceptible to viral infections, as demonstrated by chronic infection [76, 78, 79]. Chronic colonisation by bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* is also observed in a subset of patients with COPD and is associated with increased airway and systemic inflammation and exacerbation risk [80]. During an exacerbation, patients with bacterial infections are more likely to have an increase in neutrophils in sputum samples, whereas patients with viral infections can have an increase in both neutrophils and eosinophils [81].

Special populations

A small percentage of patients with COPD (⩽5%) have α_1-antitrypsin deficiency [82], an inherited condition in which circulating concentrations of the antiprotease α_1-antitrypsin are low, undetectable or mutated, thus leaving the proteolytic effects of neutrophil elastase and other proteases unopposed [83]. Neutrophil counts are elevated in the lungs of patients with α_1-antitrypsin deficiency, but the capacity of these neutrophils to kill bacteria is impaired, and they demonstrate accelerated apoptosis [84–86].

Eosinophilic COPD is marked by the presence of elevated eosinophil counts in blood or sputum. As noted previously, this accounts for a subset of patients with COPD. The estimated proportion of patients with elevated eosinophil counts is in the range of 30% to 40% and depends on the eosinophil threshold applied and the patient population being studied [29, 45, 87, 88]. Consistent with the presence of type 2

inflammation, IL-5 has been shown to be increased in the sputum of patients with COPD who have elevated sputum eosinophil counts [89]. Sputum samples of patients with COPD have also shown elevations in granulocyte–macrophage colony-stimulating factor and RANTES, which are produced by airway epithelial cells and are involved in the recruitment of eosinophils [90, 91].

Asthma–COPD overlap is a controversial label used to describe patients with clinical features of both asthma and COPD who demonstrate airflow limitation and have symptoms such as cough or dyspnoea [92, 93]. The 2024 GOLD report on chronic obstructive lung disease moves away from asthma–COPD overlap, emphasising that the two entities are separate conditions, although they share some traits and clinical features [12]. Whether viewed separately or under an umbrella term, patients with an asthma–COPD phenotype have been historically excluded from clinical trials, limiting the evidence from which to derive treatment recommendations [93]. Cumulative data from the COPDGene study have shown that patients with asthma–COPD overlap have an increased risk of exacerbations and worse health status compared with those with COPD alone [94]. A recent study that compared bronchoscopy endobronchial biopsy findings from patients with asthma–COPD overlap, asthma, COPD, normal lung function smokers and non-smoking controls found that the inflammatory cell profile of patients with asthma–COPD overlap was distinct from that of either asthma or COPD and was dominated by the presence of macrophages [95]. Further investigation is needed to fully understand the mechanisms at play and the interactions between asthma and COPD when they co-occur.

Comorbidities

Comorbidities, including cardiovascular disease, diabetes, osteoporosis and gastroesophageal reflux, are common in patients with COPD for several reasons, including the age of the patient population and/or shared risk factors such as tobacco smoking [10, 96, 97]. Comorbidities in COPD decrease quality of life, increase risk of exacerbations and increase mortality risk [10, 97, 98]. Low-grade systemic inflammation may be a link between COPD and comorbidities, such as cardiovascular disease, metabolic syndrome and osteoporosis [73, 99]. Data from ECLIPSE, a 3-year, observational, longitudinal cohort study, demonstrated that markers of systemic inflammation were elevated in patients with cardiovascular and cardiometabolic comorbidities [10]. Higher concentrations of inflammatory markers (*e.g.*, IL-6, IL-8, fibrinogen and CCL-18) were associated with the presence of heart disease, hypertension and diabetes.

One hypothesis to explain the co-occurrence of COPD and inflammation-related comorbidities is that pulmonary inflammation "spills over" into systemic inflammation, thereby promoting the development of other conditions rooted in inflammation [100]. In COPD, the immediate response to inflammation-evoking stimuli transitions to self-perpetuating chronic inflammation [17]. Low-grade systemic inflammation is evidenced by elevated circulating concentrations of inflammatory markers (*e.g.*, C-reactive protein (CRP), fibrinogen and TNF-α) and circulating leukocytes [101]. Interestingly, systemic elevations in markers of inflammation and endothelial activation have been shown to predict future development of emphysema in healthy young adults [102].

Targeting inflammation in COPD

The continued high rates of morbidity and mortality among patients with COPD underscore the need for new treatments, particularly those targeted at ameliorating underlying inflammation and immune dysfunction. The history of treatments that primarily target inflammation in COPD is mixed. Inhaled corticosteroids, which are the most commonly used anti-inflammatory treatment in COPD, have proven to be beneficial for the prevention of exacerbations in select patients when combined with a long-acting β-agonist (LABA) or a LABA and a long-acting muscarinic antagonist (LAMA) [12]. However, corticosteroids, by virtue of their mechanism of action, do not target all inflammatory pathways active in COPD (figure 3) [103, 104]. Indeed, even at high doses, inhaled corticosteroids do not reduce neutrophil counts in the sputum of patients with COPD [105]. It is uncertain whether the clinical benefits of corticosteroids are related to their effects on eosinophilic inflammation, although eosinophil count is predictive of response to corticosteroid treatment [45, 46]. Moreover, despite some acknowledged methodological limitations within and between the included studies [106, 107], a 2023 meta-analysis of 60 randomised controlled trials reported that an elevated eosinophil count ($\geqslant$200 cells·μL^{-1}) was the strongest predictor of reduced all-cause mortality risk with inhaled therapy for COPD that contained a corticosteroid [108]. However, there is also evidence to suggest that corticosteroids have effects on macrophage phenotype and function [109]. Regardless of the precise mechanism of effect, corticosteroids are an imperfect therapy as they fail to address all components of COPD-related inflammation and increase the risk for respiratory infections, particularly with long-term use [110].

Anti-inflammatory/immunomodulatory effects have been ascribed to macrolide antibiotics (*e.g.*, azithromycin and erythromycin) and LAMAs (*e.g.*, tiotropium, aclidinium, umeclidinium and

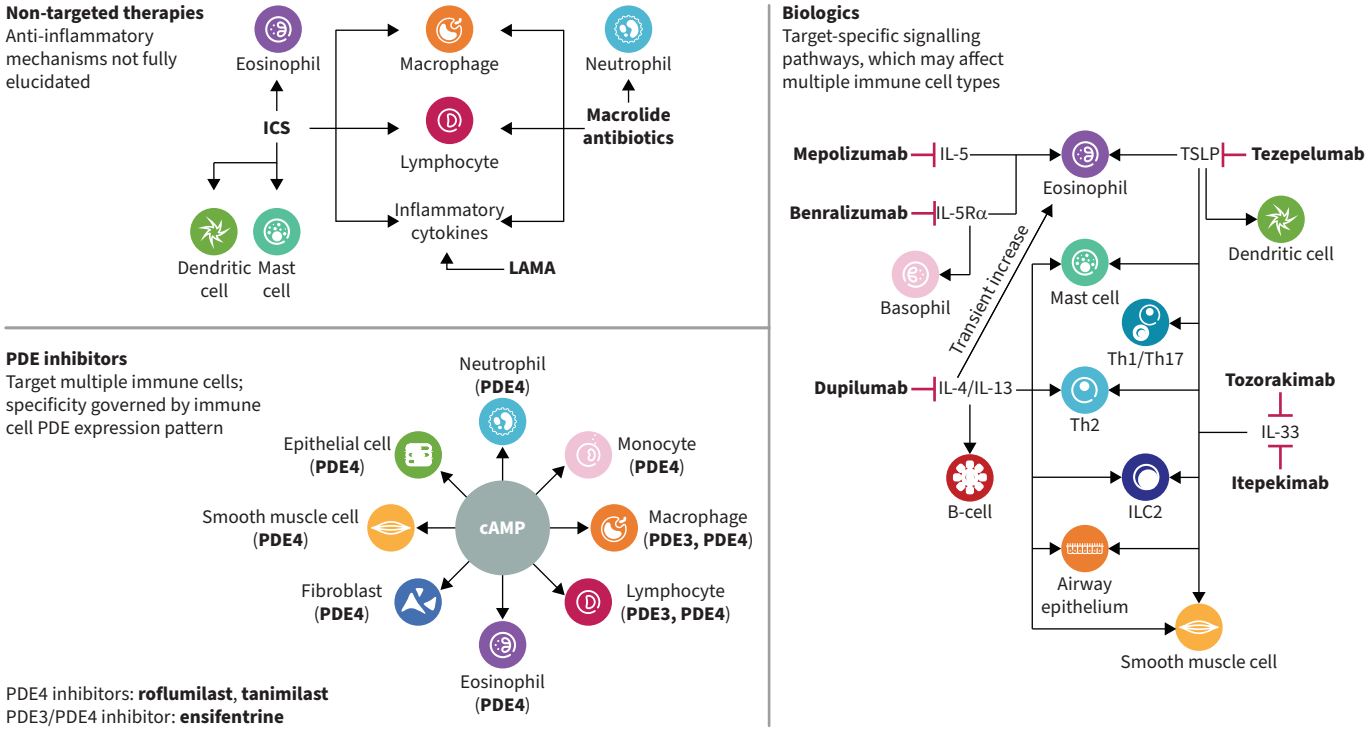

FIGURE 3 Targets of anti-inflammatory therapies in COPD [103, 104, 111, 112, 114, 119]. ICS: inhaled corticosteroids; IL: interleukin; ILC2: type 2 innate lymphoid cell; LAMA: long-acting muscarinic antagonist; PDE: phosphodiesterase; TSLP: thymic stromal lymphopoietin.

glycopyrrolate), in addition to their primary mechanisms of action, and may play a role in the clinical benefits observed with their use in inflammatory respiratory disease [111, 112]. Teasing apart the primary function of these treatments from possible anti-inflammatory effects remains an active area of investigation. Anti-inflammatory activity has also been ascribed to mucolytic agents, such as N-acetylcysteine, oral carbocysteine and erdosteine; however, the underlying mechanisms are largely unknown, and identification of a target population who may benefit from these therapies remains to be determined [12, 113]. Other treatments targeting neutrophilic inflammation (*e.g.*, TNF-α and IL-1β antibodies, p38 mitogen-activated protein kinase inhibitors) have been ineffective in treating COPD [20].

Emerging therapies that target inflammation in COPD

Biological therapies

Over the past 2 decades, there has been a tremendous expansion of biological therapy options, with approved medications for a variety of diseases, including asthma. Development has been less fruitful in COPD, for which there are currently no approved biological therapies. There are, however, several biological therapies in development for COPD. In this section, we will discuss those that have reached phase 3 clinical development, including mepolizumab, benralizumab, dupilumab, itepekimab and tozorakimab [114]. As with asthma, the majority of therapies in late-stage development target elements known to be involved in type 2 inflammation, such as IL-5, IL-4 and IL-13. In order to enrich potential responders, many studies selected patients with evidence of type 2 inflammation, often measured by the presence of eosinophilia [115–118].

Overall, the results of clinical trials have been mixed. The monoclonal antibodies mepolizumab and benralizumab reduce or deplete eosinophils by inhibiting IL-5 signalling (figure 3) [114, 119], a major player in the recruitment, proliferation, maturation and activation of eosinophils [67]. Although increases in IL-5 have been observed in patients with COPD and eosinophilia [89], mepolizumab and benralizumab have not been effective in treating COPD. Two phase 3, randomised, double-blind, placebo-controlled clinical trials (METREX and METREO) have been conducted with mepolizumab as an add-on therapy in a total of 837 patients with COPD and a history of moderate or severe exacerbations while receiving triple therapy that included a high-dose inhaled corticosteroid [115]. Patients were either stratified by baseline eosinophil count (METREX) or were required to have an eosinophilic phenotype (METREO). The primary

end-point was not met for METREO; however, in METREX, a reduction in the annualised rate of moderate or severe exacerbations was observed with mepolizumab *versus* placebo in patients with an eosinophilic phenotype ($\geqslant$150 cells·μL^{-1} at screening or $\geqslant$300 cells·μL^{-1}in the year prior) [115]. In a meta-analysis of data from both studies, reductions in exacerbation rates were greater for patients with higher eosinophil counts [115, 120]. The MATINEE clinical trial (NCT04133909) is currently ongoing and could provide further clarification regarding the potential for mepolizumab for treating COPD. Notably, this study requires patients to have demonstrated eosinophilic inflammation [118].

The phase 3, double-blind, placebo-controlled GALATHEA and TERRANOVA clinical trials randomised a total of 2665 smokers and former smokers with moderate-to-very-severe COPD and a history of moderate or severe exacerbations despite treatment with dual or triple therapy (including an inhaled corticosteroid) to treatment with benralizumab or placebo for 56 weeks [116]. Patients were stratified by blood eosinophil count at enrolment, with a 2:1 enrichment for patients with eosinophil counts $\geqslant$220 cells·μL^{-1} [116], a threshold derived from the results of a previous phase 2 study [121]. In this study population, treatment with benralizumab did not improve the annualised COPD exacerbation rate compared with placebo [116]. Subsequent exploratory *post hoc* analyses suggested that there are patient characteristics that predict a positive clinical response to benralizumab [122, 123]; however, the study authors note that the results of this study combined with that of METREX and METREO suggest that eosinophil depletion is not an effective treatment strategy for COPD [116].

Dupilumab is a fully human monoclonal antibody that reduces type 2 inflammation by targeting the shared receptor component of IL-4 and IL-13 (figure 3) [124]. A phase 3, multicentre, randomised, double-blind, placebo-controlled clinical trial (BOREAS) was conducted with dupilumab in 939 current or former smokers with COPD who had evidence of type 2 inflammation as indicated by elevated blood eosinophil count ($\geqslant$300 cells·μL^{-1}) despite triple therapy (inhaled corticosteroid plus LAMA/LABA) [117]. In this well-defined population, which notably excluded patients with a current diagnosis or history of asthma, dupilumab treatment reduced the annualised moderate or severe exacerbation rate compared with placebo and was associated with improvements in lung function, quality of life and less severe respiratory symptoms. The reproducibility of these findings is being evaluated in a second phase 3 study of dupilumab in COPD, which is due for completion in 2024 (NOTUS; NCT04456673).

Two biological therapies that target type 1 and type 2 inflammation are currently in development, itepekimab and tozorakimab, both of which target IL-33 (figure 3) [114]. A phase 2a, randomised, double-blind, placebo-controlled, proof-of-concept study of itepekimab in patients with moderate-to-severe COPD failed to meet its primary end-point, reduction in the annualised rate of moderate-to-severe exacerbations in patients treated with itepekimab *versus* placebo [125]. Although current smokers derived no benefit from itepekimab, there was a reduction in annualised exacerbation rate and an improvement in lung function in a subgroup analysis of former smokers. Phase 3 studies of itepekimab in COPD are currently ongoing. To date, no studies of tozorakimab in the treatment of COPD have been published, although phase 3 clinical trials are in progress.

Another potential target for biological therapy in COPD is thymic stromal lymphopoietin (TSLP), a cytokine that has been shown to play an important role in the development of asthma and other allergic diseases [126]. Tezepelumab, a human monoclonal antibody that binds to TSLP (figure 3), has been shown to reduce exacerbations and mucus production as well as improve outcomes in both type 2 and non-type 2 asthma [127–129], suggesting that it may have an anti-inflammatory benefit in COPD. Phase 2 studies of tezepelumab in COPD are currently ongoing (NCT04039113, NCT05507242).

PDE inhibitors

PDE inhibitors exert their effects by preventing the hydrolysis of cyclic adenosine monophosphate (cAMP) to AMP or cyclic guanosine monophosphate (cGMP) to GMP [114]. cAMP serves as a second messenger involved in multiple pathways that regulate inflammation [130]. At normal levels, cAMP suppresses inflammation [32]. When cAMP hydrolysis to AMP is increased due to PDE abundance, the resulting decrease in cAMP activates inflammatory signalling pathways. PDE inhibition increases cAMP levels, resulting in suppression of inflammation as well as smooth muscle relaxation and bronchodilation (figure 3).

Isoforms within the PDE superfamily have preferred substrate(s) and tissue-specific expression patterns [130]. PDE3 and PDE4 are normally expressed in multiple tissues, including the lung. Cigarette smoke upregulates PDE3 and PDE4 expression and/or activity in airway cells in preclinical models, and recent data show that cigarette smoking alters the expression of PDEs in human bronchial and lung tissue [131, 132]. Increased

expression of PDE4 subtypes has also been observed in alveolar macrophages and lung tissue of patients with COPD [133].

Roflumilast is an orally administered PDE4 inhibitor that has been shown to decrease neutrophilic and eosinophilic inflammation and reduce the occurrence of exacerbations when used in conjunction with other treatments [134, 135]. In patients with COPD, roflumilast reduces neutrophil and eosinophil counts in sputum, as well as concentrations of IL-8 and neutrophil elastase [134]. In clinical practice, roflumilast use is limited by side-effects, including nausea, headache and gastrointestinal issues, which have been attributed to systemic inhibition of PDE4 [32, 130].

In order to avoid the systemic exposure that is believed to cause the side effects associated with the orally administered PDE4 inhibitor roflumilast, two new PDE inhibitors delivered through inhalation, tanimilast and ensifentrine are in development for the treatment of COPD. Tanimilast is a PDE4 inhibitor, whereas ensifentrine is a dual PDE3/PDE4 inhibitor. Data have been published for two phase 2 clinical trials of tanimilast. The first study was a three-period, placebo-controlled, double-blind, crossover study that included 61 patients with COPD and a history of chronic bronchitis who were receiving inhaled triple therapy [136]. Treatment with tanimilast did not reduce the number of neutrophils, eosinophils or lymphocytes in sputum, but there was a significant reduction in macrophages compared with placebo ($p<0.05$). There were also significant decreases observed in LTB4, IL-8, MIP-1β, MMP-9 and TNF-α with tanimilast *versus* placebo in sputum samples ($p<0.05$). The phase 2b PIONEER study was a double-blind, placebo- and active-controlled, dose-ranging clinical trial that randomised 1130 symptomatic patients with COPD and a history of moderate-to-severe exacerbation to treatment with tanimilast, budesonide or placebo as an add-on to LABA therapy for 24 weeks [137]. Changes in the primary end-point measure, predose FEV_1, were small in all treatment groups, and no dose-response with tanimilast treatment was observed. Tanimilast was well tolerated in both clinical trials, without the gastrointestinal issues observed with roflumilast [136, 137], and phase 3 clinical trials of tanimilast for the treatment of COPD are currently ongoing (PILASTER, NCT04636801; PILLAR, NCT04636814).

Two phase 3, randomised, double-blind, placebo-controlled clinical trials of the dual PDE3/PDE4 inhibitor ensifentrine (ENHANCE-1 and ENHANCE-2) [138] followed demonstration of improved lung function in patients with COPD and reduced inflammatory cell counts in a model of COPD-like inflammation in phase 1 clinical trials [139], as well as positive phase 2 clinical data with ensifentrine as monotherapy (with inhaled corticosteroid therapy maintained if pre-existing) [140, 141] or add-on therapy to LAMA [142]. In the phase 3 clinical trials, patients with moderate-to-severe symptomatic COPD were randomised to treatment with inhaled ensifentrine 3 mg or placebo twice daily as monotherapy, as an add-on to LABA (with or without an inhaled corticosteroid), or as an add-on to LAMA (with or without an inhaled corticosteroid) for 24 or 48 weeks [138]. Ensifentrine significantly improved lung function at Week 12 ($p<0.001$; the primary end-point). Improvements observed with ensifentrine were consistent regardless of background therapy and occurred in patients with or without chronic bronchitis. Patients treated with ensifentrine *versus* placebo also experienced a lower annualised rate of moderate or severe exacerbations ($p<0.05$) and a delay in time to first moderate or severe exacerbation ($p<0.05$). Ensifentrine was well tolerated, with similar adverse event rates to that of placebo and a low occurrence of gastrointestinal disorders. Regulatory approval for ensifentrine in the treatment of COPD is currently pending, and an ongoing clinical trial is testing the effects of ensifentrine on sputum markers of inflammation in patients with COPD (NCT05270525).

Clinical measurement of inflammation/inflammatory biomarkers

In the research setting, a multitude of inflammatory and other biomarkers have been shown to have prognostic value, aligning with COPD disease severity or exacerbation risk [35, 143]. For example, plasma fibrinogen has been designated a qualified prognostic or enrichment biomarker for use in studies evaluating exacerbations or all-cause mortality in COPD [144]. Circulating N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentration, a biomarker used in the clinical setting for heart disease, has been shown to predict respiratory exacerbation risk and poor clinical outcomes after an exacerbation in patients with COPD [145–147]. A current area of interest and active research is the use of the neutrophil-to-lymphocyte ratio as a marker of outcomes in COPD, including exacerbations and mortality [148–150]. Measurement of fractional exhaled nitric oxide (*F*ENO) over time has been proposed as a prognostic indicator of individual patient risk in COPD [151], based on its association with IL-13 and exacerbations [152–154]. However, further study is needed before a "FeNOtyping" approach can be applied in practice [151].

There are currently limited applications for biomarkers in COPD diagnosis or prognosis. The notable exceptions are eosinophil counts and CRP. The 2024 GOLD report advocates using a blood eosinophil

count threshold of $\geqslant 300$ cells·μL^{-1} as a guide for adding inhaled corticosteroids to long-acting bronchodilator treatment [12]. The American Thoracic Society guidelines endorse this recommendation but limit its application to patients with a history of $\geqslant 1$ exacerbations in the past year [155]. Guidance regarding CRP is in the context of defining an exacerbation. An international panel of experts in COPD drafted the Rome Proposal, which, among its recommendations, suggests using a serum CRP threshold of $\geqslant 10$ mg·L^{-1} to differentiate mild from moderate exacerbations [156]. A randomised controlled trial in the primary care setting found that using CRP to guide treatment decisions for managing moderate COPD exacerbations had utility for antibiotic stewardship (*e.g.*, fewer antibiotic prescriptions in the low CRP group) without any untoward effects on COPD-related health status or treatment failure [157]. Further research into biomarkers to guide treatment decisions in COPD would be beneficial for patients and clinicians.

Conclusions

Various components of inflammation contribute to the clinical, functional and morphological expression of COPD. Evidence from clinical trials and preclinical studies points to the need to treat the underlying inflammation in COPD in order to improve patient outcomes. Appreciation of the dynamic, multifaceted and heterogeneous nature of inflammation in COPD has fostered the development of new molecular targets and refinements of existing approaches, several of which show promise as future treatment options.

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