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Immune-Modulation in Chronic Obstructive Pulmonary Disease: Current Concepts and Future Strategies

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Abstract
Chronic obstructive pulmonary disease (COPD) is caused by the chronic inhalation of toxic particles and gases that are primarily but not exclusively derived from cigarette smoke that may be either actively or passively inhaled, which initiates a persistent innate and adaptive immune response in the lung. This immune response is associated with an aberrant tissue repair and remodeling process that results in varying degrees of chronic inflammation with excess production of mucus in the central airways and permanent destruction of the smaller conducting airways and gas exchanging surface in the peripheral lung. Currently, the primary aims of treatment in COPD are bronchodilation (inhaled short- and long-acting β-agonist and antimuscarinic therapies), to control symptoms and nonspecific broad-acting anti-inflammatory agents (inhaled and oral corticosteroids, phosphor-di-esterase inhibitors, and macrolides). That provide symptomatic relief but have little or no impact on either disease progression or mortality. As our understanding of the immune pathogenesis of the COPD improves, available immune modulation therapies have the potential to alter or interfere with damaging immune pathways, thereby slowing relentless progression of lung tissue destruction. The purpose of this brief review is to discuss our current understanding of the immune pathogenesis of both the airways and parenchymal injury as well as the dysfunctional tissue repair process to propose immune modulating interventions in an attempt to stabilize or return these pathological changes to their normal state. The ultimate goal of the immune modulation therapy is to improve both morbidity and mortality associated with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a collective term for a wide spectrum of diseases involving both the large and small airways as well as the lung parenchyma. COPD is currently the fourth leading cause of chronic morbidity and mortality in the United States, and of all the leading killers, COPD is one of the only diseases where mortality rates are still rising. The World Health Organization projects that COPD will be the third leading cause of mortality worldwide in 2020 [1]. The etiology of COPD is based on a chronic inflammatory immune process that starts in the smaller conduct-

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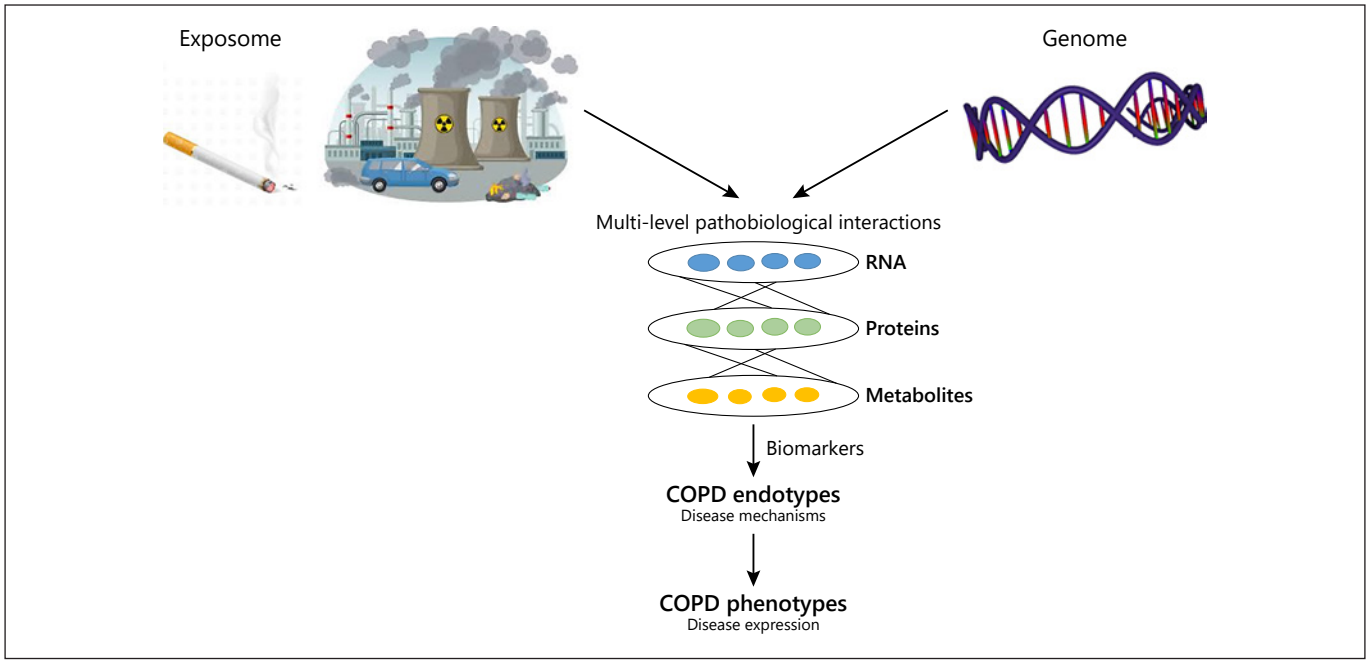

Fig. 1. Gene – environmental interaction causing disease endo/phenotypes of COPD. COPD, chronic obstructive pulmonary disease.

ing airways of the lungs and spreads into the parenchyma where it produces several different phenotypes of emphysematous destruction. That progresses in a large proportion of subjects even after they have stopped smoking. Research over the last 20+ years has focused on characterizing the nature of the inflammatory and remodeling responses in the airways and lung tissues in COPD, in an effort to design targeted therapeutics to minimize the ravages of the disease. Several of therapeutic interventions currently in use for COPD, such as bronchodilators, inhaled corticosteroids (ICS), macrolides, and phosphodiesterase inhibitors (PDE4 inhibitors), have provided symptomatic relief from the ravages of this aggressive tissue injury and repair process in COPD, but to date none have been shown to significantly impact the progressive nature (decline in forced expiratory volume in one second [FEV_1] over time) or mortality of the disease. The global impact of COPD continues to provide impetus to search for inflammatory mechanisms or pathways that can be attacked therapeutically. Better investigative techniques to unravel the complex inflammatory milieu in COPD could path the way for more targeted novel therapeutic agents (small molecules or biologics) to alter the progressive inflammatory nature of disease and ultimately the outcomes in COPD. This review will focus on the immune-inflammatory nature of COPD, current and potential novel inflammatory pathways that have the potential to be therapeutically modulated with the goal to improve COPD morbidity and mortality.

COPD Endotypes

Although COPD is a complex and heterogeneous lung condition, diagnosis, management, and treatment guidelines are empiric and still based on relatively simple clinical measurements (airflow limitation, exacerbation frequency), rather than the basic pathobiological mechanisms (endotype) of the disease process responsible for disease development and progression [2]. Most chronic human diseases, such as COPD, are rarely caused by a single gene defect but involved multiple genes that interact with many different molecular networks of proteins and metabolites, frequently modified by an environmental trigger that results in the clinical disease phenotype (Fig. 1). At biological level, the disease may express different subtypes or endotypes that could be identified by biomarkers (i.e., objective measurement of a normal biological process or state, pathogenic process or pharmacological response to a therapeutic intervention) [2, 3]. The concept of COPD endotypes has emerged from a deeper understanding of the pathobiology of airways and lung parenchymal disease that allow for more direct and precise immune modulation therapy. Molecular network analysis (…omic's) offers a platform to explore the mo-

lecular complexity of a particular disease, identify disease pathways, and explore molecular associations between distinct disease phenotypes. Therefore, network medicine has the potential to identify new gene variants that cause or are associated with disease, epigenetic changes that impact gene expression, downstream changes in proteins and metabolism with biological importance for phenotypic disease expressions, and identify drug targets and biomarkers for a complex disease such as COPD. For example, the nature of airway inflammation can vary considerably between patients with stable COPD or COPD with frequent exacerbation. Eosinophilic inflammation, which is common in subjects with asthma, is a feature of airways inflammation in significant portion of COPD patients for which ICS or biologics against the interleukin (IL)-5 cascade are potential effective treatment options in contrast to patients with predominantly neutrophilic inflammation where ICS is more likely to be ineffective or even a risk for serious adverse outcomes such as development of pneumonia and mortality [4]. This endotype is therefore a subtype of COPD defined by a distinct pathophysiological mechanism (T-helper type 2 [Th2]-driven eosinophilic airways inflammation). In contrast to endotypes, phenotypes are not necessarily linked to specific biological mechanisms (endotypes), while many can actually correspond to several endotypes (e.g., frequent exacerbators, patients with cardiovascular comorbidities). Linking endotypes to clinical phenotypes and to endotype-specific biomarkers is crucial, since phenotypes and biomarkers are more accessible to clinicians than endotypes. One well-recognized subset of COPD, alpha-1 antitrypsin deficiency, meets all of these criteria for an endotype. Other potential COPD endotypes are evolving such as COPD with persistent systemic inflammation, COPD characterized by airways colonization (and altered lung microbiome) with or without bronchiectasis [5], or COPD with a predominant Th2 immune inflammatory responses characterized by eosinophilic airways inflammation and systemic eosinophilia. Like COPD caused by alpa-1 trypsin deficiency, these endotypes could be amenable to specific immune-modulation therapies. Other potential endotypes that are less well defined worthy of further investigation are COPD patients with associated comorbidities such as sarcopenia and muscle wasting that share molecular pathways and may constitute shared therapeutic targets [6]. Similarly, COPD patients that develop lung cancer could be a specific endotype [7]. COPD patients with a significant amount of emphysema have a much higher risk of developing lung cancer than those without [8, 9], suggesting a synergistic effect between and emphysema pathogenesis and lung cancer. The molecular mechanisms linking emphysema and lung cancer development are not known, but the chronic immuno-inflammatory response that characterizes COPD is most likely a key to the pathogenesis of both diseases. Moreover, improvements in our understanding of these complex molecular networks that characterize such associations are essential to design effective immuno-modulation therapeutic strategies for these distinct "endotypes." A systems biology approach for the understanding and eventual therapeutic modification of these complex molecular, functional, clinical and environmental networks offers the possibility of a better understanding of disease pathobiology and different disease endotypes and could facilitate the development of novel therapeutic interventions.

Pathobiology of COPD

The chronic exposure to inhaled toxic gases and particulate matter are important primary etiologic triggers for the development of COPD, but there is substantial variation in the host response to these harmful environmental insults. These exposures cause both large and small airway inflammation, a hallmark of the underlying pathology in COPD [10]. This airways inflammatory response spread to the lung parenchyma resulting in destruction of alveolar walls causing emphysema [11]. Inflammatory mediators resulting in persistent infiltrating immune inflammatory cells and their destructive enzymes have been implicated in the progressive destruction of the lung in COPD [12]. This destruction initiate remodeling that has been described in both the central airways, distal airways, and lung parenchyma. It is a process of structural changes involving hyperplasia of airway epithelial cells, thickening of the reticular basement membrane, deposition of collagen, peribronchial fibrosis, airway epithelial-to-mesenchymal transition, and bronchial smooth muscle cell hyperplasia [10]. In COPD, remodeling of the small airways is an early event that spreads to the parenchyma and contributes to the development of emphysema [10]. Small airway remodeling results in obliteration of small airways and are largely responsible for the airway flow limitation seen in COPD patients. However, the underlying mechanisms underlying this sequence of events remain unclear and the topic of intense investigation. An overarching hypothesis is that oxidative stress (external and endogenous) from the inhalation of noxious gases and particles triggers a complex inflammatory response in the airways and lung tissues that eventually leads to well-described pathology of COPD

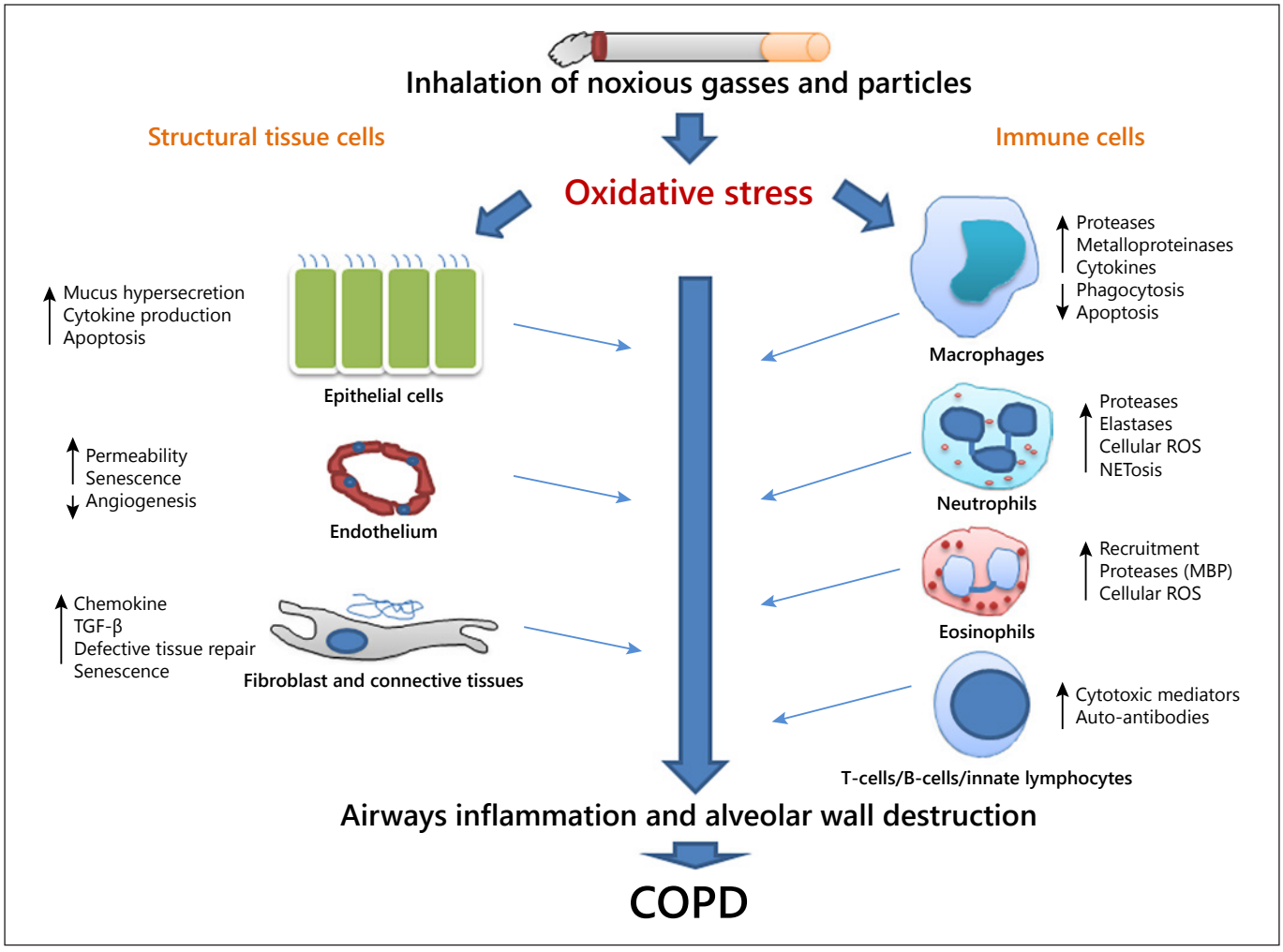

Fig. 2. Pathogenesis of COPD. COPD, chronic obstructive pulmonary disease.

(Fig. 2). Understanding the mechanistic underpinning of this process is pivotal for targeted immune-modulating therapy in COPD.

Inflammatory Cells in COPD Pathogenesis

The innate immune response to the inhalation of toxic particles and gases increases the traffic of macrophages and neutrophils into the damaged tissues. These infiltrating inflammatory immune cells control the first line of defense against the inhalation of toxic particles and gases, which includes the presentation of antigens to the dendritic cells and macrophages that activates the adaptive immune response [13]. This ongoing innate immune response and, in particular, the downstream adaptive immune response contribute to the continuation of tissue destruction following the cessation of chronic smoking [14]. Macrophages are located in airways, alveoli, and the lung interstitium. They have the ability to modulate acute and chronic inflammatory responses [15]. They are one of the main sources of cytokines and inflammatory mediators in the airways, and in addition to phagocytosing particles, bacteria, and apoptotic cells [16]. Furthermore, the production and secretion of these mediators from these macrophages also promote accumulation of other inflammatory cells such as neutrophil, a key component of the chronic innate immune response in COPD [17]. Neutrophils migrate out of the pulmonary capillaries and into the air spaces and kill ingested opportunistic microbes (fungi, protozoa, bacteria, viruses) with their armamentarium of reactive oxygen species, antimicrobial proteins, and degradative enzymes such as elastase [18]. Excessive production and release as well as inadequate

neutralization of these potential tissue damaging molecules have been shown to contribute to tissue damage and destruction in COPD [19]. Lymphocytes participate in both the innate and adaptive immune responses in COPD. Lymphocytes are found in both airways and lung parenchyma and divided into 2 major populations: thymus-dependent T cells and bone marrow-dependent B cells. T cells have 2 major subsets (CD4+ and CD8+ with further division into Th1 and Th2) and drive cell-mediated immunity, while B lymphocytes produce immunoglobulins. Thl-cells are key in providing cellular immunity and Th2 cells humoral immunity. Th2 cytokines include IL-4, IL-5, IL-9, and TL-13 and promote IgE and eosinophilic responses, currently recognized as a distinct endotype in COPD [20]. A dysregulated Thl/Th2 response is linked to a diversity of chronic inflammatory airways conditions such as asthma and chronic bronchitis. CD8+ T cells secrete molecules that kill infected cells and tumor cells. Natural killer (NK) cells are a subset of T cells with no antigen-specific receptors and NK T cells, which have similar properties as NK cells, serve to combat bacteria, protozoa, and viruses [13]. The histological analysis of COPD lung tissues showed that remodeling and destruction of the bronchiolar and alveolar tissue are associated with excessive infiltration with macrophage, CD4, CD8, and B cell and formation of tertiary lymphoid organs [21]. Interestingly, gene set enrichment analysis in COPD tissues infiltrated with CD4, CD8, and B cells showed that genes known to be expressed by NK cells, lymphoid tissue inducer, and innate lymphoid cell 1 (ILC1) cells (but not ILC2 or ILC3 cells) were enriched in COPD tissues [22, 23]. This suggests that innate lymphocytes contribute to the emphysematous destruction in COPD potentially driven by a Th1 response activated by infiltrating ILC1, NK, and lymphoid tissue inducer cells. Targeting these Th1 pathways could potentially attenuate the progressive nature of lung tissue destruction in COPD.

Structural Cells in COPD Pathogenesis

Inflammatory cells are pivotal in initiating and modulating acute and chronic airway inflammatory responses, however structural tissue cells such as epithelial, endothelial and mesenchymal cells, have a central role to amplify and modulate the inflammatory process initiated by immune inflammatory cells [24, 25].

Airway Epithelium

The respiratory epithelium responds to environmental insults (such as cigarette smoke or air pollutants) by producing and secreting chemokines, cytokines, and antimicrobial peptides [25–27] that control the trafficking of immune inflammatory cells (such as neutrophils and macrophages) into the airspaces. In addition, the bronchial mucosa consists of a mucociliated, pseudostratified epithelium with predominantly ciliated cells as well as mucus-secreting goblet cells in the large airways and basal cells/Club cells in the smaller airways that provide a physical and chemical barrier to neutralize and remove inhaled toxins and particles. These cellular secretions contain mediators that regulate inflammation, impacting chemotaxis, and antimicrobial defense by regulating oxidative/proteolytic balances [28, 29]. Airway epithelial cells also initiate and regulate the both the innate and adaptive immune responses via pattern-recognition receptors and transepithelial immunoglobulin transport [30]. These complex processes are dysfunctional in chronic inflammatory airway diseases (such as COPD), leading to altered epithelial integrity and disruption of the physical and chemical barrier functions of the lung surface [30].

Endothelial Cells

There is increasing evidence that the pathogenesis of COPD is linked, in part, to activation and eventual apoptosis of pulmonary capillaries, a key component in the pathogenesis of alveolar wall damage and destruction in the development of emphysema [31, 32]. To support this notion, Gordon et al. [33] demonstrated that smokers and, to a greater extent, smokers with early evidence of lung destruction (normal spirometry but low diffusing capacity or DLCO) have elevated levels of circulating endothelial microparticles (EMPs) or exosomes. Importantly, a significant proportion of these EMPs is derived from pulmonary capillaries and has the characteristics of apoptotic EMPs; that is, they are derived from lung endothelial cells that have been induced to undergo apoptosis. Interestingly, circulating levels of EMP drop to levels observed in nonsmokers when persons with preserved lung function stop smoking but not in patients with established COPD, suggesting ongoing alveolar wall damage in patients who have established COPD after they stopped smoking [34]. The observation of endothelial apoptosis in the lungs of humans with emphysema is well documented. There is increased DNA fragmentation in the pulmonary capillaries and arteriolar endothelium of subjects with COPD and increased alveolar endothelial and epithelial cell death in human emphysematous lungs compared with lungs of nonsmokers or smokers without emphysema. Lung levels of alveolar epithelial-derived vascular endothelial growth factor that support endothe-

lial health are decreased in emphysema, contributing to the complex mechanisms of pulmonary capillary endothelial destruction [32]. These increase levels of EMP can be detected in early COPD (GOLD I and II) before significant changes in lung density of emphysema on HRCT chest [34]. Therefore, EMP could be useful early marker of lung damage in COPD and provides potential target for early therapeutic intervention to preserve endothelial health.

Mesenchymal Cells

Several elegant studies have shown that small airways are destroyed and disappear contributing to airflow limitation and dysfunction early in the development of COPD [35]. Part of the destructive, inflammatory processes induced by noxious gases and particles (such as cigarette smoke) that ultimately lead to COPD, results from a failure of repair and remodeling and/or the regenerative processes in the lungs. There is growing enthusiasm for using progenitor or stem cells to regenerate small airway and alveolar tissue and thereby restore lung function in patients with COPD [36]. Studies in animals have revealed that human lung stem cells may contribute to distal lung tissue regeneration [37]; therefore, administration of stem cells deriving from exogenous sources may be an innovative way to treat COPD. Alternatively, advances in mesenchymal stromal cell (MSC) therapy have made this approach a strong candidate for clinical use in the treatment of COPD [38]. These cells can be obtained from a diversity of tissues and expanded with high efficiency. These MSCs have been shown to have potent immunosuppressive properties with the potential to modulate the immune inflammatory responses in the lung. Although the precise role of these cell-based treatment of subjects with COPD and specifically emphysema is still in its infancy. Encouraging outcomes of MSCs as adjuvant therapy combined with other treatments (such as endobronchial valves placement) [39] has shown benefits in pulmonary function improvement, quality of life measures, and they reduces biomarkers of systemic inflammation [40]. Cell-based therapy holds promise for future treatment of chronic lung diseases such as COPD. Stromal- or mesenchymal cell-based therapies are immunomodulatory in nature and closer to clinical implementation, and we are awaiting well-designed clinical trials to determine their role in COPD.

Mediators in COPD Pathogenesis

Immune inflammatory cells produce and secrete small polypeptide molecules (cytokines) that initiate and control the host response to injury. That are secreted by a variety of cells that include cells from the innate and adaptive immune system, as well as structural cells (epithelial and mesenchymal cells). These chemokines and cytokines can be divided into those that are proinflammatory TNF-α, IL-1, IL-13, IL-6, IL-8, and IFN-λ, which stimulate the immune system to manage and control infectious and acute toxic (such as cigarette smoke) insults. This inflammatory response involves inflammatory cells such as neutrophil and monocyte that express and release enzymes involved in matrix degradation [41]. Important anti-inflammatory cytokines include IL-10, TGF-β, and IL-lrα, secreted by alveolar macrophages that downregulate this lung inflammatory responses [42]. IL-10 also inhibits the production of proinflammatory cytokines by activation of T cells, NK cells, and monocytes [43, 44]. Dysregulation of this balance cytokine response has been shown in several chronic pulmonary diseases including COPD, for example, low levels of IL-10 are related to the severity of COPD [45]. The chronic persistent insult to the lung may contribute to this dysregulated cytokine response. For example, COPD is associated with increased local and systemic levels of TNF-α, IFN-y, IL-Iβ, IL-6, and GM-CSF, all proinflammatory cytokines, with IL-4 and IL-13 levels shown to be elevated in central airways of smokers with chronic bronchitis, when compared to those of asymptomatic smokers [46]. IL-18, a proinflammatory cytokine, has been shown to be produced intracellularly and secreted by activated macrophages [47] serving as a cofactor for both Th1 and Th2 cell development. Serum levels of IL-18 in COPD patients and smokers have been demonstrated to be elevated and negatively associated with the predicted FEV_1, when compared to nonsmokers. The highest serum levels were found in patients with COPD GOLD stages III and IV [48]. In summary, these studies demonstrate that expression and secretion of various ILs are altered in COPD, but further studies are needed to define their pathophysiological roles and whether blocking these pathways alters the inflammatory response in lung tissues. Immune-modulating therapies targeting a dysregulated cytokine network in COPD could impact disease progression.

The Lung Microbiome

In the last decade, molecular techniques that identify bacterial DNA have revealed the presence of microbial genetic material in the lower respiratory tract, previously thought to be "sterile." The characterization of this lung microbiome has advanced our understanding of the in-

teraction of the lung microbiota with the local and systemic immune systems, through which it modulates the immune response in the context of health and a variety of respiratory diseases, in particular airways diseases such as asthma, COPD, and bronchiectasis [49]. Advances in microbiota characterization have shed light on lower airways colonization in a variety of chronic airway disease, including COPD, implicating decreased airway clearance that facilitates selective microbial growth resulting in colonization [50, 51]. There has also been advances in the understanding of how microbes in the lower airways interact with each other and their microenvironment. Hilty et al. [49] showed that distinct lower airway microbiota is reflective of airway inflammation without clinical respiratory infection, which suggests that the microbiota composition can be indicative of airways disease. Microbial interactions with airway surfaces contribute directly or indirectly (by altering the mucosal immune responses) to airway damage, resulting in airways inflammation, increased airways secretions, and reduced mucociliary dysfunction compromising airway clearance causing disease progression [52]. Therefore, the composition of the lung microbiome that is altered in COPD, further change during acute exacerbations, and with the use of steroids and/or antibiotics provide a window of opportunity to determine the impact of the lung microbiome on disease development and progression, which could ultimately lead to novel immune-modulating therapies.

Immune Modulation with Current COPD Therapies

Current treatment strategies for COPD consist of bronchodilation, anti-inflammation, and antiinfection therapeutic agents. These treatments clearly improve COPD symptoms, but currently, there is very little evidence that any of these approaches to treatment have the potential to reverse airway remodeling and consequently irreversible obstructive airflow. Currently, just cessation of smoking has convincingly been shown to reduce the decline in FEV_1 over time.

Corticosteroids

Anti-inflammatory treatment has the potential to alter the airways and lung tissue inflammatory response impacting tissue damage and remodeling. In a recent study, Toczyska et al. [53] compared anticholinergics to inhaled corticosteroid and showed the ICS could reduce reticular basement membrane thickening and inflammatory cell infiltration in airways tissues from patients with COPD. Further the observation that treatment with ICS changes vessel density and epithelial-mesenchymal transition suggests the possibility that it might be able to influence airway remodeling. However, as airflow limitation was not changed over the 12-month study period, suggesting that long-term studies are needed to determine the potential beneficial effects of ICS on airways remodeling.

In a subgroup of COPD patients with prominent Th2-eosinophilic airways disease, there is reasonably good evidence that these patients respond to corticosteroids and possibly to blockers of cytokines produced by Th2 cells. Typically, these patients have milder COPD, get frequent exacerbations, and are characterized by sputum and/or blood eosinophilia. Systemic corticosteroids in a group of COPD patients with elevated sputum eosinophils improve symptoms, postbronchodilator FEV_1, and shuttle walk [54]. These benefits of systemic steroids also apply to ICS, implying that sputum eosinophils can serve as a biomarker of this endotype to the targeted use of inhaled corticosteroid in COPD [55, 56]. These studies suggest that blood eosinophils, which is much easier to measure, could be a surrogate for sputum eosinophils, especially with persistent eosinophilia above >300 cells/μL. A small randomized trial of benralizumab (an anti-IL-5 receptor alpha blocker) showed that in patients with COPD and serum eosinophil counts ≥300 cells/μL improved lung function (FEV_1) and reduce exacerbations, suggesting that blocking the Th2 cytokines in subjects with eosinophilic/Th2 high COPD is a reasonable option [57]. A recent larger randomized trial in subjects with COPD and blood eosinophil counts >220 cells/μL followed for a year, showed a trend in reducing exacerbations rate in the group receiving the higher dose of benralizamab (100 mg very 4 weeks) but no significant difference in overall exacerbations rates between groups [58]. Although disappointing, these studies highlight the importance of better phenotyping and endotyping subjects in future studies exploring different Th2 cytokines blockers as immune modulations of airways inflammation in COPD.

Macrolides

Chronic bacterial colonization of the airways correlations with the extent of airway inflammation in stable COPD [59]. The immune host responses induced by bacterial colonization are thought to contribute to COPD progression and is marked by elevated inflammatory markers such as C-reactive protein, IL-1β, IL-8, TNF-α in lung tissue. Antibiotics could reduce bacterial load in airway that is related to COPD severity and pro-

gression. Recent meta-analysis of the use of macrolides in reducing COPD exacerbations showed a significant reduction in acute exacerbations COPD (AECOPD; OR 0.28 95% CI 0.12–0.68) with low dose of macrolides continuously over the full year of the study [60]. This provides evidence of clinical benefit using macrolides as immune modulators in COPD. Macrolides are known to have immunomodulatory effects on airway remodeling. Macrolides suppress activator protein 1 and the NF-κβ-mediated inflammatory cascade resulting in reduced IL-1, IL-6, IL-8, TNF-α in COPD patients. Macrolides impact a wide variety of immune and structural cells. They reduce adhesion molecule expression by pulmonary epithelium and endothelium, thereby reducing neutrophil and macrophages recruitment, first-line innate immune cells that contribute to airway remodeling. Macrolides also reduce the expression of neutrophil adhesion molecules Mac-1 (CD11b), reduce neutrophil chemotaxis, and reduce the serum concentration of soluble adhesion molecules, such as sL-selectin, sE-selectin, and sP-selectin [61]. Macrolides promote monocyte-to-macrophage differentiation, enhance phagocytosis of apoptotic cells by macrophages, thus reducing further inflammatory responses related to cell necrosis, alter macrophage phenotype to improve bacterial clearance, and enhance macrophage cytocidal activity in COPD [62–64]. Macrolides also reduce monocyte-macrophage differentiation, MMPs production, and protease activity [59]. Macrolides, such as azithromycin, reduce the risk for COPD exacerbation, which is accompanied by a reduction in plasma sTNFrII, suggesting that they also reduce the systemic inflammatory response associated with COPD. New macrolide derivatives with enhanced anti-inflammatory properties and less antimicrobial activity have recently been developed to reduce the chances of bacterial resistance documented with long-term use of macrolides in COPD. A novel class of nonantibiotic 14-membered macrolide derivatives of azithromycin with anti-inflammatory and immune-modulatory effects, attenuate lung inflammation, and diminished the production of proinflammatory cytokines by macrophages exposed to *Pseudomonas aeruginosa* LPS in mice [65]. Solithromycin (CEM-101) is a novel macrolide fluoro-ketolide, with good antimicrobial activity and also displays superior anti-inflammatory profiles compared with other macrolides currently used. It is able to restore corticosteroid sensitivity by inhibition of PI_3K signaling under oxidative stress [66]. More recently, another novel 12-membered nonantibiotic macrolide, EM900, has been shown to inhibit rhinovirus (RV) infection by reducing the ICAM-1 levels on epithelial cells and thereby modulates the airway inflammation associated with RV infections [67, 68]. Considering RV is the major cause of COPD exacerbation, macrolides such as EM900 could be a candidate drug for the prevention of COPD exacerbation. In addition, EM900 has been documented to exert direct inhibitory effects on mucus secretion from airway epithelial cells [69]. These findings collectively indicated that these novel macrolides hold great promise for the treatment of COPD in the future, while maintaining the benefits of macrolide use without increasing the risk of antimicrobial resistance. Combining macrolides with steroids also improves corticosteroid sensitivity through inhibiting the PI3K-δ/Akt pathway and enhancing glucocorticoid receptor α expression [70]. Therefore, combining macrolides with corticosteroids might enhance the anti-inflammatory effects of steroids in the treatment of COPD. Macrolides also influence the adaptive immune responses by downregulating the expression of the costimulatory molecule CD40 on dendritic cells thereby inhibiting the differentiation of Th17 cells induced by dendritic cells [71]. Collectively, understanding the immunomodulatory mechanisms of macrolides and its derivative may open a new window for the immune-modulating treatment of COPD in the future.

Phosphodiesterase Inhibitors

The nonselective PDE inhibitors (methylxanthines) and theophyllin are older medications that remain in use because they have both bronchodilator and anti-inflammatory affects via inhibition of PDE4 and histone deacetylase-2 activation [72]. The PDE4 enzyme family is encoded in 4 different genes (PDE4A to D), they hydrolyze cAMP, and are expressed in T-cells, B-cells, and innate immune cells such as macrophages, eosinophils, and neutrophils, as well as airway epithelial cells and endothelial cells [73]. Therefore, the action of selective PDE4 inhibitors is predominantly anti-inflammatory and immune modulating [74]. In contrast, the newer second-generation PDE4 inhibitors, such as roflumilast, are able to decrease airway hyperreactivity by reducing the production and release of TNF-α, and possibly slow tissue destruction by inhibiting specific matrix metalloproteinases. Moreover, their clinical benefit may be primarily based on their ability to inhibit chronic lung inflammation in asthma and COPD [75, 76]. Last, their beneficial effects on blood vessel disease, in subjects with COPD, may be an additional benefit in subjects with cardiovascular comorbidities.

Future Strategies in Immune Modulation in COPD

Immume Modulation in Eosinophilic/Th2-High COPD

Strong recent evidence suggests that a subgroup of patients with COPD who have marked sputum and/or blood eosinophilia may respond to corticosteroids and possibly to blockers of cytokines produced by Th2 cells [55, 77, 78]. This beneficial effect extends to ICS as well; therefore, sputum eosinophils may be a useful biomarker to predict what a COPD patient may respond to ICS. Several studies have shown that blood eosinophilia, which is much easier to obtain, could be a useful surrogate for sputum eosinophils, especially if the blood eosinophilia is persistently high (>200 cell/μL). This represents a substantial portion of COPD patients (37%) in the ECLIPSE cohort [79]. Th2 cytokines, including IL-5, IL-4, and IL-13, could drive eosinophilic inflammation in this COPD endotype. Therefore, identifying this subgroup of COPD and target the eosinophils with either corticosteroids or specific Th2 blocker may prove to be a step toward precision or personalized targeted treatment in COPD.

Immune Targeting Cytokines in COPD

COPD is characterized by progressive airway and lung tissue inflammation, with AECOPD frequently driven by infections (bacterial or viral) that augment this inflammatory response. This chronic inflammation of the airways has been shown to play a key role in the pathogenesis and progression of COPD. There is a growing interest in targeting inflammatory mediators such as cytokines or chemokines in attenuating the chronic inflammatory response in the airways and slowing the destructive process in lung tissues in COPD [80]. The Th2 cytokines (IL-4/IL-5/IL-13) are the primary targets for current available biologic therapeutics in chronic airway diseases associated with a more eosinophilic inflammatory response. These biologics have been extensively studied in the more eosinophil airways disease of asthma with the anti-IL-5 mepolizumab, the first to show a reduction in eosinophils, acute exacerbations, and the need for systemic steroids in asthma, and more recently, 2 additional anti-IL-5 antibodies (Reslizurnab and Benralizuinab) have been cleared by the FDA for their safety and efficacy in reducing asthma exacerbations [81–83]. IL-5 therapeutics are currently in COPD clinical trials, and both Benralizurnab and Mepolizurnab are currently in phase 3 trials with Benralizumab displayed a beneficial effect on lung function [57] but did not reduce acute exacerbation rates [58], while treatment with mepolizurnab has been shown to reduce exacerbations [84]. An anti-IL-4 antibody is currently under late clinical trial phases for asthma. The IL-4 receptor inhibitor that also modulates IL-13, Dupilurmab, has shown notable improvements in exacerbations and lung function in eosinophilic airways disease from asthmatic patients [85], and studies in COPD are ongoing. The anti-IL-13 inhibitors, Lebrikizurnab and Tralokinurnab, showed less promise in phase 3 clinical trials for asthma, while studies with an inhibitor of TSLP (Tezepelumab) show more promise in phase 3 trials reducing exacerbations and blood eosinophil counts [80]. The role for biologics that target the Th2 response in the Asthma/COPD overlap syndrome with a prominent eosinophilic inflammatory response still needs to be determined.

The primary innate immune cytokines, TNF-α, IL-1β, and IL-6, are all involved in the inflammatory response to inhaled aeropollutants and are naturally attractive targets in modulating the inflammatory response in COPD. Inhibition of TNF-α has been studied quite intensively in several chronic inflammatory diseases including airways disease such as asthma and COPD, however, with limit success. IL-1 is a proinflammatory cytokines with increased expression in COPD that further increase during exacerbations [86], but small clinical trials with IL-1β blocking antibody (Canakinumab) and a recombinant IL-1ra protein (Anakinra) for COPD were disappointing. Blocking antibodies against the IL-6 receptor (Tocilizumab) has been studied in other inflammatory diseases such as rheumatoid arthritis and Crohn's disease, revealing decreased IL-6 levels, but it has not been tested in inflammatory airway diseases yet. Therefore, targeting IL-6 could be a potential novel and promising treatment strategy to suppress not only chronic airway but also its associated systemic inflammation, COPD-associated frailty, and decline in lung function. In COPD, targeting these mediators could have potential serious side effects as it attenuates the innate immune responses against viral and bacterial infections, culprits in triggering exacerbations of COPD.

IL-8 has also been characterized as a key potential contributor to the development of COPD. The COPD bronchial epithelium has been shown to have a higher baseline expression of IL-8, thus leading directly to mucus hypersecretion by induction of the mucin genes MUC5AC and MUC5B [87, 88]. IL-8, an important cytokine involved in neutrophilic inflammation, is elevated with AECOPD [89], with circulating IL-8 being negatively associated with lung function [90]. A significant portion of COPD subjects have prominent neutrophilic airways inflamma-

tion; therefore, IL-8 is an attractive target to reduce neutrophil recruitment [91]. Inhibitors of the IL-8 chemokine receptor, CXCR2, involved in neutrophil recruitment, is an attractive target to decrease neutrophilic inflammation. A CXCR2 antagonist, Danirixin, is currently being examined for clinical usage in COPD [92]. The impact of biologics, to impact the cytokine and chemokine inflammatory milieu in COPD to reduce airways and tissue inflammation in stable COPD and during an exacerbation, is still in its infancy and an evolving field of research.

Immune Modulation Targeting Proteases

One of the most damaging major proteases released from neutrophils is elastase with α-1-antrypsin, the major neutralizer of excess elastase. Alpha-1 antitrypsin (A1AT) deficiency meets all of the criteria for a distinct endotype of COPD. It has a known genetic underpinnings, distinct clinical and histopathological characteristics, distinct epidemiology, and a mechanism-directed proven treatment approach that is guided by biomarkers (serum A1AT level, A1AT protein phenotyping, and A1AT genotyping) and physiological parameters (FEV_1). Intravenous augmentation treatment has been shown to be disease modifying with evidence that this slows decline in FEV_1 and emphysema determined by CT density measurement [93–95]. New user-friendly immune modulation using inhaled alpha-1-antitrypsin (PhaseII trail) is currently underway [96]. There is paucity of data around other treatments specific for COPD, in general, and their efficacy in AATD. Inhalation of noxious gases and particles also activated macrophages, which produce matrix metalloproteinases and cysteine proteinases that promote lung inflammation, degrade extracellular matrix proteins, and injure alveolar septal cells to cause airspace enlargement [97]. Modulating metalloproteinases by neutralizing or decreasing expression and/or release is therefore an attractive target in attenuating airways and lung tissue inflammation in COPD. Interestingly, Polverino et al. [98] recently showed that the disintegrins or metalloproteinase domain-8 and 9 (Adam 8 and 9) have opposite effects [98, 99]. Deficiency in these proteinases showed a resistance to the development of emphysema in a mouse model of CS-induced emphysema. They also showed decrease expression on lung macrophages in human studies, which has been associated with reduced macrophage apoptosis (causing increase macrophages numbers in the lung) and promotion of integrin mediated recruitment of immune cells such as neutrophils. The lack of Adam8 expression on lung epithelial cells causes decrease in EGFR shedding leading to mucus cell metaplasia, increase in alveolar cell apoptosis, and impairs alveolar septal repair. Together these downstream effects will promote airways disease and emphysema and they postulate that the immune modulation of the disintegrins, Adam 8 and 9, to increase or prolong their expression on cell surfaces may have potential as a novel therapeutic for patients with COPD to slow progression of disease.

Immune Modulation Targeting the Lung Microbiome

The recognition the last decade, of the importance of the lung microbiome in modulating both the local and systemic immune systems, has fuelled the interest in altering the lung microbiome to modulate the inflammatory response in various respiratory diseases. Therefore, the characterization of the lung microbiome has the potential to provide new therapeutic options to manipulate the lungs pathophysiological mechanisms of homeostasis. Changes in the lung microbiome, and, consequently, this homeostasis are known as dysbiosis, which has been characterized in a variety of lung diseases such as cystic fibrosis, COPD, asthma, and interstitial lung diseases [100–103]. In COPD, bacterial colonization is common and thought to contribute to persistent airways immune and inflammation responses. It has been postulated to contribute to the progression of COPD and FEV_1 decline and increasing the risk for exacerbation [104]. The pleiotropic effects of antibiotics, particularly those of the macrolide class that also have anti-inflammatory properties [105], led to their use in the prevention of exacerbations. Whether this benefit is due to the antibacterial effect of azithromycin on bacterial colonization or more direct anti-inflammatory effects is uncertain. The long-term effects of chronic azithromycin therapy on the lung microbial community, however, are yet to be determined although initial reports suggest that while the overall bacterial burden remains stable, the alpha diversity of the lung decreases significantly [106]. With acute exacerbation of COPD, antibiotics covering pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae,* and *Moraxella catarrhalis* have become mainstays of therapy, and numerous trials have confirmed their beneficial effects [107, 108]. However, the notion that all acute exacerbations must be treated with antibiotics is questionable. To better identify the subset of AECOPD subjects who could benefit from antibiotics, several studies have explored biomarkers such as procalcitonin [109], C-reactive protein, and neutrophil CD64 expression [110] to identify subjects that may benefit from antibiotic treatment. These biomarkers may still find their way into clin-

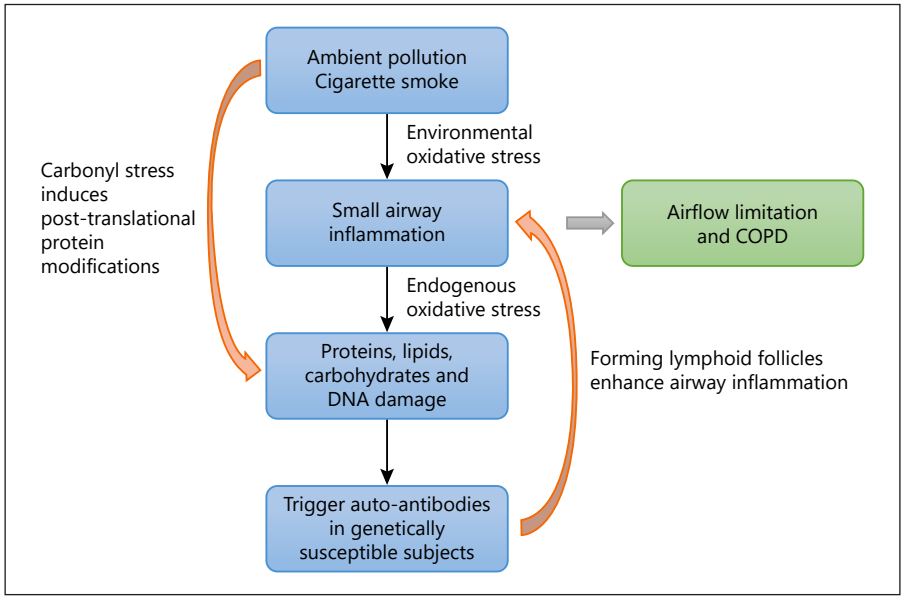

Fig. 3. Oxidative (ROS) and nitrosative (RNS) stress from both environmental and endogenous sources combined with environmental carbonyl stress damage and modify proteins, lipids, carbohydrates, and DNA-producing neoantigens, triggering autoantibodies in susceptible subjects. This results in autoimmune inflammation and tertiary lymphoid follicle formation enhancing small airways inflammation and progressive damage and destruction of these airways, a hallmark of COPD. COPD, chronic obstructive pulmonary disease.

ical decision algorithms. The role of pathogenic microbes triggering AECOPD has been extensively investigated and well established, but the clinical significance of airways colonization in COPD pathogenesis remains less clear. The question of whether colonizing microbes actively contribute to COPD pathogenesis, or whether they altered immune responses observed in stable versus colonized COPD contribute to COPD pathogenesis, still needs to be established. The characterization of the lung microbiome and its downstream immune response in the airways, in both its acute exacerbations of COPD and in chronic stable COPD, has the potential to reveal previously unrecognized therapeutic and prognostic markers that have the potential to predict disease outcome or infection susceptibility.

Immune Modulation Targeting Small Airways

The small conducting airways (<2 mm in diameter in adult human lungs) have been shown to be an early target for the immune inflammatory response induced by inhalation of toxic particles and gasses such as cigarette smoke, resulting in COPD [21]. As the disease progresses, the infiltration of inflammatory immune cells is dominated by lymphocytes that form lymphoid follicles with germinal centers, characteristic of an adaptive immune response that include macrophages and dendritic cells, B-cells, and plasma cells surrounded by T cells (referred to as either lymphoid neogenesis or tertiary lymphoid organ formation) [111]. These observations have led to the notion that autoimmunity has a role in the pathogenesis and progression of COPD. It is postulated that neoantigens are generated by environmental triggers (such as cigarette smoke, air pollutants, or biomass) via oxidative stress pathways that induce damage to lipids, proteins, carbohydrates, or DNA. Either environmental or endogenous oxidative stress may also cause the formation of carbonyl stress that through posttranslational, nonenzymatic modifications of proteins result in the formation neoautoantigens triggering an autoimmune response in the small airways of susceptible subjects. This causes local activation of cell-mediated autoimmune damage and remodeling to the small airways [112] (Fig. 3).

These autoimmune pathways are potential targets for therapeutic intervention by immune modulating drugs. Although ICS treatment of COPD is rather ineffective in reducing airway inflammation and lung function decline, withdrawal of ICS in stable patients with COPD results in an increase in CD3, 4 and 8 positive T cells in the bronchial mucosa [113]. This suggest that ICS could reduce the airways adaptive immune response in COPD, specifically in patients with increased B-cell activity (such as patients with high autoantibody titers) [114]. This suppression of airways B-cell responses may also be responsible for the increased risk of pneumonia seen in COPD patients treated with high doses of inhaled glucocorticoids [115]. The B-cell activating factor (BAFF), which is responsible for B-cell survival and maturation, is overexpression in autoimmune diseases [116], as well as overexpressed in small airway lymphoid follicles in COPD compared to control smokers, postulated to create a self-perpetuating loop

(promoting B-cell survival) contributing to COPD progression [117]. Blocking BAFF in a mouse model of cigarette-induced pulmonary emphysema attenuates airways inflammation and alveolar destruction [118]. Belimumab, a monoclonal antibody against BAFF that reduces B-cell differentiation and survival, has been approved for subjects with systemic lupus erythematosus [119] and shown to impact B-cells function in a mouse model of emphysema [120]. The therapeutic potential of blocking BAFF in subjects with COPD still needs to be explored. A Th17 response is part of the immune inflammatory response in the smaller airways in COPD. It induces B-cell maturation and facilitates neutrophils and macrophage recruitment for mucosal immunity. High levels of IL-17A are strongly linked to the development of autoimmune disorders. In the smaller airways of COPD, 5% of IL-17A comes from Th17 cells and the rest from CD31+ endothelial cells [13]. Modulators of the Th17 immune response (anti-IL-17A mAB) have been approved for psoriasis [121] and have therapeutic potential in subjects with COPD [14, 115]. Last, the local microbiota in the small airways could promote chronic pulmonary inflammation by enhancing IL-17A overexpression and the subsequent synthesis of autoantibodies [122, 123]. The interplay between the local microbiome and the innate and adaptive immune responses is now recognized to be a specialized form of a field immune response designed to protect epithelium in the gut, airways, urinary tract, and skin, which is of considerable interest for future studies of chronic lung disease such as COPD. Autoimmunity is likely to play a more central role in the progression of COPD in certain COPD endotypes (rather than an unifying central role) and drugs that target this autoimmune response are available. The results of well-designed controlled clinical trials, modulating autoimmune pathways, are of great interest.

Immune Stimulation as Immune Modulator in the Airways

The pathobiology of airways disease in COPD is associated with alterations in the normal mucosal immune responses that render it vulnerable for colonization and eventual invasion of pathogenic microorganisms. Therefore, enhancing or boosting the airways mucosal immune responses in subjects with COPD, to attenuate colonization of airways and/or invasion of viral or bacterial microorganisms into airways tissues, is a logical therapeutic option. One such compound is OM-85 (Broncho-Vaxom®), an oral medicine of biological origin used for the prevention of recurrent respiratory tract infections in at-risk populations. This immune stimulator has been shown to be effective and safe in both children and adults [124, 125]. OM-85 is an extract of bacterial lysates isolated from 21 common known respiratory pathogens that has been shown to trigger immunomodulatory and protective immune responses against diverse pathogens in vivo [124, 126], including influenza and respiratory syncytial virus as well bacterial superinfection following influenza [127]. The mechanisms of action of OM-85 have been comprehensively explored and appear to be via modulation of the inflammasome and stimulation of Th1 immune responses in the mucosa [128, 129]. Recent meta-analysis of all the RCT trails in COPD (~1,000 subjects) showed a significant reduction in AECOPD (20 and 39% reductions in exacerbation rate [RR 0.80; 95% CI 0.65–0.97; $p = 0.03$] and incidence rate of patients using antibiotics [RR 0.61, 95% CI 0.48–0.77; $p < 0.0001$] compared with the placebo). These are small studies, and we need more solid evidence to confirm the benefit of this immune modulation strategy, however, with better phenotyping and endotyping of COPD patients, this novel therapeutic intervention could be beneficial for subjects with predominantly airways disease, particularly if the airways are chronically colonized.

Immune Modulation of the Systemic Inflammatory Response in COPD

Inflammation in COPD has airway and systemic components [130, 131]. The systemic inflammatory response in COPD is associated with a rapid decline in lung function [132], increased mortality [133], and a higher exacerbation rate [134, 135]. Studies by Fu et al. [136] showed that the presence of systemic inflammation, measured by elevated systemic C-reactive protein and IL-6, is predictive of future exacerbations in asthma and COPD. They show that systemic inflammation was associated with elevated IL-1β expression in the airways, and this airway-systemic inflammatory axis was predictive of COPD exacerbations. Therefore, targeting the mediators involved in the systemic inflammatory response associated with COPD has the potential to slow progression of the disease and reduce exacerbations of COPD. In addition, there are convincing evidence that the comorbidities associated with the COPD, which impact COPD morbidity and mortality, are strongly related to this systemic inflammatory response [133, 137]. Therefore, targeting the systemic inflammatory response in COPD is a reasonable option for future therapy to impact COPD progression and exacerbations.

Conclusions

Although our understanding of the cellular and molecular mechanisms underlying COPD has improved in recent years, they are complex and in general remain poorly understood. Current therapy has little if any effect on either disease progression or mortality. This is partly due to COPD being a complex heterogeneous disease, which is expressed in a variety of disease phenotypes. These different phenotypes have different profiles of disease progression and are associated with different comorbidities. It is reasonable to postulate that that these different phenotypes also have different cellular and molecular mechanistic underpinnings, which could explain why there is currently no therapeutic intervention that significantly and broadly reduces either disease progression or mortality. The mainstay of management of COPD disease is that long-acting bronchodilators have minimal effects on the underlying chronic inflammatory response in the lung. In addition, a significant portion of COPD subjects are essentially resistant to broad-spectrum anti-inflammatory molecules such as corticosteroids. Thus, there is an obvious need for novel anti-inflammatory therapies that can act on new promising molecular and/or cellular targets with the promise that modulating the immune inflammatory response in the lungs of COPD subjects will slow the progression of the disease and ultimately reduce mortality. Future studies should focus on a better understanding of the pathobiology of COPD. These studies should include longitudinal study of the endotypes or biomarker-defined subgroups to better understand the characteristics and stability of these subgroups.

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