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REVIEW

Cytokine inhibition in the treatment of COPD

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Abstract: Cytokines play an important part in many pathobiological processes of chronic obstructive pulmonary disease (COPD), including the chronic inflammatory process, emphysema, and altered innate immune response. Proinflammatory cytokines of potential importance include tumor necrosis factor (TNF)-α, interferon-γ, interleukin (IL)-1β, IL-6, IL-17, IL-18, IL-32, and thymic stromal lymphopoietin (TSLP), and growth factors such as transforming growth factor-β. The current objectives of COPD treatment are to reduce symptoms, and to prevent and reduce the number of exacerbations. While current treatments achieve these goals to a certain extent, preventing the decline in lung function is not currently achievable. In addition, reversal of corticosteroid insensitivity and control of the fibrotic process while reducing the emphysematous process could also be controlled by specific cytokines. The abnormal pathobiological process of COPD may contribute to these fundamental characteristics of COPD, and therefore targeting cytokines involved may be a fruitful endeavor. Although there has been much work that has implicated various cytokines as potentially playing an important role in COPD, there have been very few studies that have examined the effect of specific cytokine blockade in COPD. The two largest studies that have been reported in the literature involve the use of blocking antibody to TNFα and CXCL8 (IL-8), and neither has provided benefit. Blocking the actions of CXCL8 through its CXCR2 receptor blockade was not successful either. Studies of antibodies against IL-17, IL-18, IL-1β, and TSLP are currently either being undertaken or planned. There is a need to carefully phenotype COPD and discover good biomarkers of drug efficacy for each specific target. Specific groups of COPD patients should be targeted with specific anticytokine therapy if there is evidence of high expression of that cytokine and there are features of the clinical expression of COPD that will respond.

Keywords: airway inflammation, COPD, exacerbations, new drugs, cytokine blockers

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a:

> … common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.[1]

COPD is currently one of the most important causes of morbidity and mortality worldwide, and is predicted to become the third-leading cause of death by 2020. The estimated annual costs of COPD in the US are ~$50 billion, and most of these costs are related to exacerbations requiring hospitalization.

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The etiology of COPD appears to point to interactions between environmental factors (particularly cigarette smoking) and genetic factors.[2] Chronic cigarette smoking is currently the cause of more than 90% of cases of COPD in Westernized countries,[1,3] but recent studies have described a significant prevalence of COPD amongst never-smokers. In some countries, such factors as environmental indoor pollution from the use of coal or biomass fuel consumption may be an important cause.[4]

The pathological hallmarks of COPD are destruction of the lung parenchyma with pulmonary emphysema, inflammation of the small airways with respiratory bronchiolitis, and inflammation of the central airways with chronic bronchitis.[5–7] The progressive chronic airflow limitation in COPD is likely to result from two major pathological processes: remodeling and narrowing of small airways, and destruction of the lung parenchyma, with the consequent loss of the alveolar attachments of these airways.[8] Both small-airway remodeling and narrowing and pulmonary emphysema are associated with chronic inflammation in the lung periphery.[8,9] Pulmonary emphysema usually only appears with increasing severity of COPD, and can also be present, even severe and diffuse, in subjects without airflow obstruction.[10] When emphysema is moderate or severe, loss of elastic recoil becomes overwhelmingly important, and thus may mask the effects of bronchiolar disease on chronic airflow limitation. By contrast, when emphysema is mild, the contribution of bronchiolar abnormalities to chronic airflow limitation is evident.[11]

Many patients with COPD have chronic bronchitis with increased sputum production. The presence of chronic bronchitis may be a predictor of COPD-related death, increased risk of pneumonia, and accelerated decline in lung function.[12,13] The pathophysiological relationships between airway mucus secretion and COPD are complex. Mucus is the main component of sputum, and its specific viscoelastic and rheological properties are due to the presence of mucins, which are large high-molecular-weight oligomeric glycoproteins. Mucins are the main component of lower-airway mucus, and several mucins (including MUC2, MUC5AC, MUC5B, MUC6, and MUC8) are secreted in the lower airways.[14–16] Airflow obstruction in COPD is caused by small (peripheral) airway lesions, and their intraluminal amount of mucus is increased[17] and correlates with the degree of severity of stable COPD.[9]

Such comorbidities as cardiovascular disease, metabolic syndrome, osteoporosis, depression, lung cancer, and skeletal muscle dysfunction are now recognized to have an important negative impact on quality of life and survival.[18] Other considerations in the pathophysiology of COPD include the development of pulmonary hypertension from hypoxic vasoconstriction and the emphysematous process, and the occurrence of exacerbations, the frequency of which is usually increased with disease severity and triggered mainly by infections, but also by other such factors as particulate pollution.[19]

Airway and lung inflammation is a predominant feature of COPD.[2,8] Although cigarette smokers who do not have COPD have a degree of inflammation, those with COPD have a far greater degree of inflammation that progresses with advancing disease,[9] sometimes accompanied by systemic inflammation, and inflammation in other nonpulmonary organs, such as the heart, blood vessels, and skeletal muscle.[18] Squamous dysplasia is a feature of cigarette smokers that may be a precursor to the development of non-small-cell lung cancer. Apoptosis remains a potential mechanism underlying alveolar destruction, with breakdown of extracellular matrix in lung parenchymal tissues. Conversely, there is an increase in extracellular matrix in the small airways.[7]

On the basis of currently available treatments and their effects, the objectives of treatment are to reduce symptoms and to prevent and reduce the number of exacerbations. These goals are achievable, but preventing decline in lung function can be more difficult and is probably not achievable currently. Bronchodilators form the backbone of symptomatic treatment, and the improved long-acting β_2-agonists and anticholinergics, possibly in combination, provide the best form of bronchodilator therapy for COPD, with the additional effect of reducing the exacerbation rate.[1] The addition of inhaled corticosteroids to bronchodilator therapy is advocated for patients with frequent exacerbations, particularly those with more advanced disease. There has been no other addition to current treatment options for COPD apart from the recent introduction of the phosphodiesterase-4 inhibitor roflumilast, which may be useful in reducing exacerbations in patients with severe airflow obstruction and chronic bronchitis.[1] Although current developments are focusing on improved once-daily combinations of bronchodilators and corticosteroids, perhaps the most promising approach to finding agents that will stop disease progression or even prevent the decline in lung function and reverse the disease process is to block aspects of the inflammatory and remodeling processes.[20] Targeting specific cytokines may be important in this.

Overview of inflammation in the pathogenesis of COPD

The cellular inflammation in stable COPD is characterized by the presence of increased numbers of macrophages,

neutrophils, T lymphocytes, dendritic cells and B lymphocytes.[5–8] Increased numbers of neutrophils and B lymphocytes are usually associated with the most severe COPD.[5,8] During COPD exacerbations, there is also a recruitment of eosinophils, particularly during virus-induced severe COPD exacerbations.[21] T lymphocytes in COPD are predominantly $CD8^+$, but $CD4^+$ cells are also increased. T-helper (Th)-1 and T-cytotoxic (Tc)-1 subtypes, characterized by production of interferon (IFN)-γ, predominate,[5] although Th2 cytokines are also increased in stable COPD patients with increased interleukin (IL)-4 expression in $CD8^+$ cells (Tc2 cells) from bronchoalveolar lavage (BAL).[22] In the blood, there are increased proportions of $IFN\gamma^+$ and $TNF\alpha^+$ $CD8^+$ T-cells in stable COPD patients correlating with Global initiative for chronic Obstructive Lung Disease grades when compared with healthy never-smoking controls.[23] An increased number of Th17 cells is also present in bronchial biopsies of patients with stable COPD.[24]

Many inflammatory cells and mediators are involved in the inflammatory process of COPD. It is clear that cigarette smoke itself can directly activate many cells, such as epithelial cells or macrophages, to release cytokines and chemokines, leading to inflammatory cell recruitment and activation and to tissue destruction.[2] TNFα, IL-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), and CXCL8 (IL-8) are released by airway epithelial cells exposed to cigarette smoke,[2,25] in addition to transforming growth factor (TGF)-β1, which is implicated in the activation of myofibroblasts and airway smooth-muscle cells to cause proliferation and fibrosis.[26] Alveolar macrophages are also activated by cigarette smoke extract to release a similar profile of cytokines as epithelial cells, including TNFα, CXCL8, CCL2 (monocyte chemoattractant protein [MCP]-1) in addition to leukotriene B_4 and oxidants (reactive oxygen species).[25,26] Alveolar macrophages, like bronchial epithelial cells, can also release a number of other chemokines, including CXCL9 (monokine-induced by IFNγ), CXCL10 (IFN-inducible protein 10) and CXCL11 (IFN-inducible T-cell alpha chemoattractant), which are chemotactic for CD8 T cells through the CXCR3 receptors.[25] In addition, there is the synthesis of elastolytic enzymes, such as matrix metalloproteinase-2 (MMP-2), MMP-9, MMP-12, and cathepsins.[27] Regulation of these cytokines is likely to be under the control of nuclear factor (NF)-κB, which is activated in macrophages from COPD patients.[28] An increased number of macrophages in the lungs is probably due to increased recruitment of blood monocytes to lungs or due to increased local proliferation and survival of lung macrophages.[25]

There are increased numbers of neutrophils in sputum and BAL in COPD, and their numbers correlate with disease severity.[6] Chemotactic signals for neutrophil recruitment include leukotriene B_4, CXCL1 (previously known as growth-related oncogene [GRO]-α), CXCL2 (GROβ), CXCL3 (GROγ), CXCL5 (epithelial neutrophil-activating peptide 78), and CXCL8, the expression of which is increased in COPD, and likely to be derived from alveolar macrophages and epithelial cells.[25] GM-CSF and granulocyte CSF may increase the survival of neutrophils.[25]

There is now increasing interest in the participation of the inflammasome in COPD, which could be the origin of some cytokines. The inflammasome's primary role is defending against invading pathogens, including bacteria and viruses. The innate immune system is characterized by its ability to recognize and respond to an array of infectious agents and endogenous molecules, such as double-stranded deoxyribonucleic acid and extracellular adenosine triphosphate released during cell and tissue injury. This is mediated through the detection of these pathogen-associated and danger-associated molecular patterns by receptors termed pattern-recognition receptors. These include the Toll-like receptors (TLRs), the intracellular retinoic acid-inducible gene-like helicases, and the intracellular nucleotide-binding oligomerization domain-like receptors (NLRs). NLRs are characterized by three domains, including an N-terminal interaction domain that mediates protein–protein interactions with downstream signaling intermediates and that can be used to categorize the NLRs into five subfamilies: NLRA (containing an acidic transactivation domain), NLRB (containing a baculovirus inhibitor of apoptosis protein repeat), NLRC (containing a caspase-recruitment domain), NLRP (containing a pyrin domain), and NLRX (containing an unknown domain). NLRs respond to pathogen-associated and danger-associated molecular patterns through the formation of inflammasomes: multimeric cytoplasmic protein complexes that act as molecular platforms for the activation of inflammatory caspases following stimulation by foreign agonists. A typical inflammasome is composed of an NLR, an adaptor protein, such as apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC), and an effector caspase that activates proinflammatory cytokines, in particular IL-1β and IL-18. Three NLR proteins have been shown to form inflammasomes: NLRP1, NLRP3 (NALP3, also known as cryopyrin or pyrin-containing Apaf 1-like protein 1), and NLRC4 (also known as Ipaf). Stimulation of the NLRP3 leucine-rich repeat domain by a foreign agonist is postulated to unfold the NLRP3 molecule, enabling

recruitment of the ASC adaptor proteins and procaspase 1. Thus, the inflammasome acts as a platform for the autoproteolytic cleavage of procaspase 1 to produce active caspase 1, which in turn cleaves pro-IL-1β and pro-IL-18 to promote their secretion in conjunction with the alarmin high-mobility group box 1.[29] In COPD, there is evidence of an increase in the number of CD8 T-cells expressing TLRs 1, 2, 4, 6, and TLR2/1, with only TLR2/1 increased on lung CD4 T-cells and TLR2 on CD8 natural killer T-cells.[30] There is evidence that TLRs are involved in the release of cytokines, such as IL-12 and IL-17 from T-cells.

There is a very long list of cytokines and chemokines that have been implicated in the many facets of the pathogenesis of COPD. Some of these have been supported through genome-wide association studies on COPD, lung function, and COPD complications.[31] Proinflammatory cytokines of importance include TNFα, IFNγ, IL-1β, IL-6, IL-17, IL-18, IL-32, and thymic stromal lymphopoietin (TSLP). Several chemokines are also involved, but these have been recently reviewed[24] and so will not be reviewed here, outside of CXCL8, which has traditionally been considered as a cytokine. Among the growth factors, we will review the role of TGFβ superfamily and other profibrotic growth factors with more published data on their potential role in the pathogenesis of COPD.

Individual cytokines involved in the pathogenesis of COPD

IL-1

Both IL-1α and -β bind to a single IL-1 receptor (named IL-1R1), and are proinflammatory cytokines produced mainly by monocytes, macrophages, and fibroblasts.[32,33] Mice lacking IL-1R1 have reduced neutrophilic inflammatory response to cell death, but not to a bacterial infection, and decreased tissue damage from inflammation, whereas the acute monocyte response to cell death, important for tissue repair, is much less reduced,[34] suggesting that blocking the IL-1 pathway will not affect the host response to microbial pathogens. The IL-1 receptor antagonist (IL-1RN or IL-1RA) binds to IL-1R and inhibits the binding of both IL-1α and -β, neutralizing their activity, and thus acting as an endogenous counterregulatory mechanism.[35]

Cells immunoreactive for IL-1α and -β are increased in bronchial biopsies from patients with stable COPD compared to non-COPD controls,[36] even though this finding for IL-1β was not recently confirmed.[29] There are increased levels of serum, sputum, and BAL IL-1β[37–40] in patients with stable COPD. Animal models of COPD provide discordant data on the role of the NLRP3 inflammasome in driving IL-1β-modulated smoke-induced lung inflammation.[38,41,42] Originally, it was suggested that IL-1β played a role in smoke-induced emphysema and airway remodelling,[41] but more recent data in mice favor a role for inflammasome-independent induction of IL-1β in driving smoke-induced inflammation.[38,42] This is in line with a recent unpublished clinical trial showing that canakinumab, a monoclonal antibody neutralizing IL-1β, was ineffective in the treatment of stable COPD.[43] Another IL-1β blocking antibody, MEDI8986, is currently undergoing a clinical trial in COPD.[44]

IL-5

IL-5 is a cytokine produced by the Th2 lymphocytes usually associated with asthmatic airway inflammation, but may also be involved in the pathogenesis of COPD, particularly during exacerbations. Sputum levels of IL-5 protein, BAL T-cell IL-5 expression, bronchial mucosal IL-5 messenger ribonucleic acid (mRNA) and peripheral lung IL-5 protein expression in patients with stable COPD are low/absent and not different from control subjects.[45–48] Similarly, the number of IL-5$^+$ immunoreactive cells is not significantly different in the bronchial mucosa (including submucosal glands) of patients with chronic bronchitis, with or without COPD, when compared with control subjects, and interestingly, other cells (mainly plasma cells) outside of T lymphocytes are the major sites of IL-5 production.[49–51] Sputum levels of IL-5 in patients with stable COPD correlate with the degree of eosinophilia and response to glucocorticoids of these patients, suggesting that these subjects have an overlap syndrome asthma/COPD.[52,53] In addition, soluble IL-5Rα is increased during virus-induced COPD exacerbations,[54] but in patients with mild/moderate COPD during an exacerbation of the disease, IL-4 and IL-5 expression was not changed compared to stable disease.[50,55]

GM-CSF

GM-CSF is released in the COPD lung mainly from infiltrating cells.[56] Proinflammatory cytokines, such as TNFα, IL-17, and bacterial lipopolysaccharide can induce in vitro the release of GM-CSF from cells. In vitro exposure to cigarette smoke extract decreases the release of GM-CSF from bronchial epithelial cell lines,[57] and in line with this effect, a single exposure to cigarette smoke decreased lung GM-CSF mRNA in animals,[58] but in animal models, repeated cigarette smoke exposure increased lung GM-CSF expression.[59,60] In mouse models of cigarette smoke and lipopolysaccharide exposure, treatment with a neutralizing anti-GM-CSF monoclonal antibody reduced the number of BAL macrophages and

neutrophils and the lung expression of many inflammatory mediators.[61–64] In vitro stimulation of $CD8^+$ T-cells isolated from the lungs of patients with stable COPD using anti-CD3-ε antibodies activating the T-cell receptor induced the secretion of GM-CSF.[65] There are no published studies comparing if these cells isolated from the lungs of age-matched control smokers with normal lung function released different amounts of GM-CSF compared with those isolated from the lungs of patients with COPD. Sputum levels of GM-CSF, but not peripheral lung GM-CSF expression, were increased in patients with stable COPD compared to control subjects in some studies[56,66] and decreased in others.[67] There are no published studies using GM-CSF blockers in patients with COPD. MOR103 is a fully human monoclonal antibody that selectively neutralizes human GM-CSF, and is being developed in the area of inflammatory diseases, ie, rheumatoid arthritis (http://www.morphosys.com/node/2563).

IL-6

IL-6 may play an important role in the progression of COPD severity.[68] IL-6 may also contribute to the pathogenesis of the autoimmune response observed in the lungs of the patients with more severe stable COPD.[69] IL-6 is a potent inductor of C-reactive protein (CRP) production in the liver, and increased IL-6 plasma levels are associated with increased CRP levels in patients with stable COPD.[70,71] Plasma levels of IL-6 are increased in patients with stable COPD compared to controls,[72] are persistent in their duration, and may contribute to the increased risk of depression associated with COPD and also to its mortality.[73–77] However, other studies suggest that increased plasma levels of IL-6 are limited to patients with stable COPD and concomitant cardiovascular comorbidities.[78] IL-6 levels are also increased in the sputum of patients with stable COPD compared to control subjects.[79,80] Several anti-IL6 blocking antibodies have been developed and have been used in clinical trials of rheumatoid arthritis and several cancers with some efficacy,[81] but there are no data on patients with COPD. Interestingly, COPD patients who walked the most had the lowest plasma CRP and IL-6, suggesting that an intervention to promote walking may reduce systemic inflammation in COPD.[82]

Thymic stromal lymphopoietin (TSLP)

TSLP is a cytokine of the IL-7 family, is produced mainly by stromal cells, including mast cells,[83–86] and is involved in the activation, expansion, and survival of T lymphocytes and dendritic cells. TSLP expression in the airway epithelium is inducible through a NF-κB-dependent pathway.[87,88] Its action is mediated by a heterodimeric receptor composed of IL-7Rα and TSLP receptor (TSLPR). Some functions of TSLP and its receptor overlap that of IL-7 and its receptor, despite signaling predominantly through signal transducer and activator of transcription (STAT)-5 at variance with IL-7Rα, and thus this represents an alternative pathway to the IL-7/IL-7Rα axis. In human airway smooth-muscle cells, TSLPR signaling is mainly mediated by STAT3.[89]

In vitro TSLP and TSLP-R expression in human airway smooth-muscle cells is increased after chronic exposure to cigarette smoke extract,[90] and TSLP is a mediator of cross talk between airway smooth-muscle and mast cells.[91] TSLP and TSLP-R-blocking antibodies neutralize the increased contraction of airway smooth-muscle cells induced by cigarette smoke extract,[90] suggesting a role for this pathway in bronchoconstriction. TSLP has also been implicated in the induction of glucocorticoid resistance in Th cells during airway inflammation by controlling the phosphorylation of STAT5.[92] In addition, TSLP may amplify alternatively activated airway macrophage polarization and chemokine production.[93] An increased number of cells expressing TSLP mRNA has been reported in the bronchi of stable COPD patients and control smokers with normal lung function,[94] and increased TSLP immunostaining has been shown in the smooth muscle of patients with stable COPD compared to nonsmoking subjects.[95] Blocking antibodies have been developed (http://www.freepatentsonline.com/8232372.html),[96] but there have been no studies on COPD so far.

CXCL8

CXCL8 levels are markedly elevated in the sputum of patients with stable COPD, and are correlated with disease severity.[97,98] Blocking antibodies to CXCL8 and related chemokines inhibits certain types of neutrophilic inflammation in experimental animals.[99] The neutralization of CXCL8 with a blocking antibody significantly reduces the neutrophil chemotactic activity of sputum from patients with stable COPD;[100,101] however, this reduction is only partial, indicating that other neutrophil chemotactic factors, such as leukotriene B_4 and the activated complement factor C5a, are also involved.[99] However, CXCL8 plays a major role in neutrophil chemotaxis caused by alveolar macrophage-derived conditioned media, and this is most effectively inhibited by dual antagonism of CXCR1 and CXCR2 receptors.[102]

The mean sputum levels of CXCL8 are significantly higher in α_1-antitrypsin-deficient patients than in patients with COPD with normal levels of α_1-antitrypsin,[103] and enhanced CXCL8 expression is associated with increased

neutrophil chemotactic activity of sputum from patients. In addition, there is an increase in BAL levels of CXCL8 in current smokers with pulmonary emphysema and in stable COPD.[104,105] A slight, albeit significant, increase of CXCL8 protein epithelial expression is present in the bronchial mucosa of severe stable COPD patients compared to control healthy smokers.[106] In contrast, no significant differences are observed in the submucosa of stable COPD and control subjects at both mRNA and protein level,[106] suggesting a minor role of this chemokine in the bronchial mucosa of stable COPD patients.

The expression of CXCL8 mRNA and protein is increased 1.5-fold in the bronchiolar epithelium of patients with COPD compared to control subjects.[107,108] There is also increased expression of CXCR2 mRNA, a CXCL8 receptor, in the bronchiolar epithelium of COPD patients compared to control subjects, suggesting that this axis may be relevant in the recruitment of neutrophils to the small airways.[109] A monoclonal antibody against CXCL8 improved dyspnea in patients with COPD, but had no effect on lung function, health status, or 6-minute walking distance.[110] A CXCR2 antagonist (navarixin, formerly CH527123) reduced sputum neutrophils in patients with stable COPD, but has not shown any clinical benefit.[111] Another CXCR2 antagonist (AZD5069) reduced blood neutrophils in patients with stable COPD without any clinical benefit.[112] The efficacy of the oral CXCR2 antagonist danirixin (formerly GSK1325756B) is currently being investigated in a 1-year clinical trial of patients with mild-to-moderate COPD (http://www.gsk-clinicalstudyregister.com/study/200163#ps).

IL-17

IL-17, also known as IL-17A, is produced predominantly by CD4 and CD8 T-cells,[113] known respectively as Th17 and Tc17 cells, and can be induced in vitro by different combinations of TGF-β, IL-1 β, IL-2, IL-6, IL-15, IL-18, IL-21, and IL-23.[114] Human regulatory T-cells can differentiate into IL-17-producing cells when stimulated by monocytes in the presence of IL-2/IL-15.[115] Th17 cells in addition to IL-17A also release IL-17F, IL-21, IL-22, GM-CSF, and CCL20, and are critical for the clearance of extracellular pathogens, but under certain conditions are associated with the pathogenesis of several autoimmune and inflammatory diseases.[116] IL-17A induces the release of CXCL1, CXCL8 and GM-CSF from airway epithelial cells and smooth-muscle cells, and thereby may orchestrate neutrophilic inflammation.[117–119] IL-17A can induce IL-6 expression in bronchial epithelial cells and fibroblasts,[117] and IL-17A, in conjunction with IL-6, is able to induce MUC5AC and MUC5B production in primary human tracheobronchial epithelial cells.[120] IL-17A is also involved in human airway smooth-muscle contraction.[121]

Serum IL-17A levels are increased in patients with stable COPD compared to healthy smokers and nonsmokers, increase with COPD stage, and are inversely correlated with predicted forced expiratory volume in 1 second (FEV_1) percentage.[122] IL-17$^+$ neutrophils are present in induced sputum from patients with stable COPD, but it remains unclear whether the sputum levels of IL-17A are increased in patients with stable COPD.[122,123] There is a significant increase in the number of IL-17A$^+$ immunoreactive cells in the bronchial submucosa of mild/moderate and severe COPD patients compared to control nonsmokers,[24,124] and in the peripheral lungs of stable COPD patients compared to smokers with normal lung function and nonsmoking subjects.[122,125]

Anti-IL-17 antibody in cigarette smoke-exposed mice reduced IL-17 levels in lung homogenates, and reduced neutrophil response in BAL and the degree of small-airway inflammation.[126] Th17 cells have been shown to mediate glucocorticoid-resistant airway inflammation and airway hyperresponsiveness in mice.[127] In IL-17$^{-/-}$ mice exposed to cigarette smoke, neutrophil inflammation and the number of apoptotic type 2 alveolar cells were decreased.[128] IL-17RA is required for CCL12 expression, macrophage recruitment, and pulmonary emphysema secondary to cigarette smoke,[129] and also for the development of elastase-induced pulmonary emphysema,[130] but not oxidant-induced emphysema.[131] IL-17 neutralizing, as well as anti-human IL-17R (such as brodalumab) antibodies are currently available for clinical studies in COPD, having recently been reported in a study of patients with asthma.[132]

IL-18

IL-18 (previously termed IFNγ-inducing factor) is produced by alveolar macrophages and the airway epithelium. IL-18 binds to its receptor (IL-18R) subunit-α (IL-18R1),[133] but the signaling activity requires also the presence of the β-subunit (also termed IL-18R accessory protein or accessory protein-like).[134,135] In the presence of IL-12, IL-18 has an important role in Th1/Tc1 polarization. In fact, IL-12 increases IL-18R expression by Th1 cells, promoting Th1-cell polarization and proliferation, secretion of IFNγ, and macrophage and neutrophil accumulation.[135,136] However, in the absence of IL-12, IL-18 induces the release of Th2 and Th17 cytokines (eg, IL-4, IL-5, IL-9, and IL-13). IL-18 can also act as a cofactor for Th2-cell development and immunoglobulin (Ig)-E production, and also plays an important role in the differentiation of Th17 cells.[135,136] Within the

NRLP3 inflammasome complex, autocatalytic cleavage of procaspase 1 to active caspase 1 enables removal of IL-1β and IL-18 prosequences, resulting in biologically active forms of IL-18.[137,138]

IL-18 may represent a novel master cytokine regulator that can drive all of the key pathologies found in stable COPD.[139] IL-18R1 plays a critical role in the pathogenesis of cigarette smoke-induced pulmonary emphysema and inflammation.[140–142] IL-18-mediated alveolar endothelial cell death may also contribute to vascular destruction and disappearance in chronic secondhand smoke exposure-induced pulmonary emphysema.[143,144] Furthermore, transgenic mice overexpressing IL-18 in the mature lung show lung inflammation with increased numbers of $CD4^+$, $CD8^+$, $CD19^+$, and natural killer 1.1^+ cells, pulmonary emphysema, mucus metaplasia, airway fibrosis, vascular remodeling, and right ventricle cardiac hypertrophy.[145] There are increased levels of plasma and sputum IL-18[146–149] in patients with stable COPD compared to control smokers and nonsmokers. There is also an increased percentage of IL-18Rα-expressing T lymphocytes and $CD8^+$ T-cells in stable COPD patients compared with control subjects.[149] IL-18R protein expression is higher on alveolar macrophages in peripheral lungs from stable very severe COPD patients compared to control subjects.[150]

The safety of MEDI2338, a monoclonal IgG_1 antibody blocking human IL-18 (http://www.ncats.nih.gov/files/MEDI2338.pdf), in stable COPD patients has been evaluated,[151] but apparently its development has been discontinued.

IL-22

IL-22 is expressed predominantly in Th1 and Th17 cells, particularly in the presence of IL-23,[152] which is also increased in the epithelium and submucosa of stable COPD patients.[24] In animal models, IL-22 is a crucial effector molecule in host defense against Gram-negative bacterial pneumonia.[153] Serum and sputum IL-22 are significantly increased in the sputum of stable COPD patients, particularly in advanced grades, and of control smokers with normal lung function compared with nonsmoking subjects.[122] In the bronchial mucosa, immunostaining for IL-22 is localized to endothelial cells, inflammatory cells, and fibroblasts, and the number of $IL\text{-}22^+$ immunoreactive cells was increased significantly in the bronchial epithelium of severe and mild/moderate stable COPD compared to control nonsmokers, but did not differ in comparison with control smokers with normal lung function.[24] The number of $IL\text{-}22^+$ cells in the bronchial submucosa was significantly higher in severe and mild/moderate COPD compared to control nonsmokers, but did not differ in comparison with control smokers with normal lung function.[24] The proportions of blood $IL\text{-}22^+$ cells in the $CD4^+$ memory ($CD45RA–CD45RO^+$) T-cell population were significantly increased in COPD active smokers, when compared with ex-smokers.[23] Human bronchial epithelial cells also express IL-22R and IL-17, and IL-22 increases the expression of antimicrobial proteins, such as lipocalin-2, in airway epithelial cells,[154] even though in animal models neither administration of IL-22 nor of IL-22 blocking antibodies has any effect on lung neutrophilia.[155]

IL-23

In animal models, chronic cigarette smoke exposure increases the expression of IL-23 in the lungs.[156,157] In bronchial mucosa, immunostaining for IL-23 is localized in endothelial cells, inflammatory cells, and fibroblasts, and the number of $IL\text{-}23^+$ immunoreactive cells is increased in the bronchial epithelium of stable COPD patients compared with control groups,[24] but in the human lung there is no significant difference in the expression of IL-23R between COPD and control groups.[158] In contrast, the number of $IL\text{-}23^+$ cells in the bronchial submucosa was significantly higher in severe stable COPD patients compared to control nonsmokers, but did not differ in comparison with control smokers or mild/moderate stable COPD.[24] These findings are in line with a previous demonstration of increased expression of IFNγ and of STAT4, its downstream transcription factor, in bronchial biopsies from patients with stable COPD.[159] IL-23 induces the proliferation of memory T-cells and the secretion of IFNγ, and in animal models cigarette smoking increases the lung expression of IL-23.[156,157] IL-17A production by Th17 cells is induced by IL-23.[160,161] In vitro, the COPD-associated pathogenic bacteria *Haemophilus* and *Moraxella* spp. provoke a 3-5-fold higher production of IL-23 from human monocyte-derived dendritic cells compared to lung commensal bacteria,[162] suggesting a potential link between chronic bacterial colonization of the lower airways, often present in COPD,[163] and the development of lung cancer in COPD patients, eg, by amplification/perpetuation of airway inflammation, which has been linked with multiple molecular mechanisms in the promotion of lung cancer.[164] Blocking anti-IL-23 antibodies are effective against neutrophilic inflammation in several diseases and in animal models.[165]

IL-33

IL-33 is another member of the IL-1 family, and is localized to the chromatin in the cell nucleus.[166] The cytokines of

the IL-1 family – IL-1α/β, IL-1Ra, and IL-18 – have been matched to their respective receptor complexes, but the ligand for the most prominent orphan IL-1R, ST2,[167] is IL-33.[166] Three distinct types of ST2 (also termed IL-33R, IL-1RL1, T1, Fit-1, and DER4) exist; a soluble secreted form (ST2), a transmembrane receptor form (ST2L), and a variant form (ST2V). There is constitutive expression of IL-33 mRNA in bronchial smooth-muscle cells, bronchial epithelial cells, and high endothelial venule endothelial cells.[167,168] The expression of IL-33 may also be enhanced through activation of the inflammasome.[169]

IL-33R (or ST2) is selectively expressed on Th2 cells (where it stimulates the production of IL-4) and on mast cells.[167,170] Soluble ST2 receptor is considered anti-inflammatory in animal models,[171] and its plasma level is increased in mild/moderate stable COPD compared to control smokers with normal lung function.[172] In animal models after exposure to tobacco smoking, the lung expression of IL-33 and ST2 is markedly enhanced and associated with neutrophil and macrophage infiltration and expression of inflammatory cytokines (IL-1β, TNFα, IL-17), chemokines (CCL2), and MUC5AC in the lower airways. These changes are all significantly prevented by treatment with neutralizing anti-IL-33 antibody.[173]

TNFα

TNFα is an important chemotactic protein for neutrophils; in fact, the inhalation of TNFα induces sputum neutrophilia and airway hyperresponsiveness in normal subjects.[174] In vitro, TNFα also induces CCL13 (monocyte chemoattractant protein 4) expression, a chemokine with potent chemotactic activities for eosinophils, monocytes, T lymphocytes, and basophils. TNFα may also activate structural (such as epithelial and smooth-muscle cells) and inflammatory cells of the airways to release inflammatory mediators (such as oxidants).[175,176] TNFα stimulates the secretion of MUC5AC from bronchial epithelial cells,[177] upregulates adhesion–molecule expression on inflammatory, epithelial, and endothelial cells, facilitates the migration of inflammatory cells into the lower airways, and activates profibrotic mechanisms involved in airway remodeling.[175,176]

TNFα levels are increased in the blood and sputum of COPD patients.[72,97] They also have significantly higher levels of soluble TNFR1 in sputum and TNFR2 in blood. In addition, sputum sTNF receptors, but not blood sTNF receptors, are inversely related to FEV_1 in patients with COPD.[178] COPD patients also show an increased *TNFA* gene expression in their skeletal muscles.[179] The severe weight loss present in some patients with advanced COPD might also be due to skeletal muscle-cell apoptosis (muscle cachexia), as a result of increased levels of circulating TNFα.[175,180]

Glucocorticoids, low-dose theophylline, phosphodiesterase-4 inhibitors, and p38 mitogen-activated protein-kinase inhibitors potently inhibit TNFα production in vitro and/or in vivo.[181] Selective TNFα inhibitors in clinical development include nonhuman or chimeric antibodies (infliximab, afelimomab, and CytoTab), humanized antibodies (adalimumab and certolizumab pegol [CDP870]), human TNFR (onercept), or TNFR fusion protein (etanercept). TNFα-converting enzyme (ADAM17) is an MMP-related enzyme that is required for the release of soluble TNFα, and might be another attractive target. Small-molecule TNFα-converting enzyme inhibitors, some of which are also MMP inhibitors, are in development as oral TNFα inhibitors.[175,182]

Three studies of infliximab in patients with mild-to-severe COPD have reported no beneficial effects on various clinical parameters, including exacerbations, dyspnea, and FEV_1.[183–185] However, in a study of 157 patients with COPD, infliximab increased the incidence of pneumonia and malignancy, and more patients receiving infliximab had to discontinue therapy due to adverse events.[183] Systemic blockade of TNFα can lead to increased risk of infection, recurrence of tuberculosis, and reactivation of hepatitis B, as well as worsening of congestive heart failure. It has been proposed that anti-TNFα therapy may be more beneficial for COPD exacerbations than as maintenance therapy, but the TNFα blocker etanercept was found to be no more effective than prednisone in the treatment of COPD exacerbations.[186]

TGFβ superfamily and other profibrotic growth factors

The TGFβ superfamily consists of secreted growth factors involved in the regulation of different cellular processes, such as cell growth, development, differentiation, proliferation, motility, adhesion, and apoptosis.[187] Increased levels of TGFβ1 have been reported in such lung diseases as COPD, asthma, and pulmonary fibrosis.[26] TGFβ1 is highly expressed in the epithelium and macrophages of small airways in patients with COPD, but it is still not known whether this is an expression of COPD or the effect of cigarette smoking.[188–190] The bone morphogenic protein and activin membrane-bound inhibitor (BAMBI) is a membrane-spanning glycoprotein that acts as a negative regulator of TGFβ signaling.[191] BAMBI is induced by members of the TGF family – β-catenin, SMAD3, and SMAD4[191] – and acts as a pseudoreceptor.[192] In the peripheral lungs of patients with stable COPD compared with control subjects and in vitro there is a marked

upregulation of BAMBI expression (alveolar macrophages and alveolar epithelial cells) after infection ex vivo of the lung tissue with nontypable *Haemophilus influenzae* that is present in the peripheral lung tissue in around a third of patients with stable COPD, but absent in the controls.[193] Connective tissue growth factor is a cysteine-rich peptide involved in cell proliferation, migration, and extracellular matrix production.[194] Conflicting results have been reported in peripheral lung tissue from patients with stable COPD showing downregulation[195] or upregulation[196] of mRNA for connective tissue growth factor compared with control smokers with normal lung function.

There is increased cytoplasmic expression of fibroblast growth factor (FGF)-2 in bronchiolar epithelium and its nuclear localization in bronchiolar smooth-muscle cells in COPD patients compared with controls. In addition, increased FGFR-1 expression in bronchiolar smooth-muscle cells and increased FGF-1 and FGFR-1 are seen in the bronchiolar epithelium from COPD patients.[197] In COPD patients, an increase in FGF-2 expression is also observed in vascular smooth-muscle cells and the endothelium of small pulmonary vessels. In contrast, vascular smooth-muscle cells of large pulmonary vessels show increased staining for FGF-1 and FGFR-1 compared to controls.[198]

Cytokines in COPD exacerbations

IL-1β, IL-6, CXCL8, IL-10, and TNFα levels are increased in sputum supernatants during COPD exacerbations.[53,199–204] Elevated levels of IL-1β in exhaled breath condensate and sputum during COPD exacerbations, particularly when associated with bacterial infections, have been reported.[205] Bacterial exacerbation has also been associated with higher levels of sputum CXCL8 and TNFα, leading to enhanced neutrophil recruitment and activation.[186,204] Increased sputum $CD8^+$ T lymphocytes have been reported during COPD exacerbations, with a relative reduction in the ratio of IFNγ/IL-4-expressing $CD8^+$ T lymphocytes.[204] Therefore, a switch toward a Tc2-like immunophenotype during COPD exacerbations could trigger recruitment of eosinophils, and might be activated by the immune response to some microbial pathogens. However BAL CD4 T-cells from patients with COPD exacerbations exhibited a Th1 (IFNγ release) and Th2 (IL-4 release) cell–cytokine phenotype during acute infection with rhinovirus.[206]

However soluble, IL-5RA is increased during virus-induced COPD exacerbations,[54] and in animal models of COPD after exposure to rhinovirus, there is increased lung expression of IL-5.[207] In addition, patients with mild/moderate COPD during an exacerbation of the disease show an increased number of TNFα mRNA-producing cells in their bronchial mucosa in comparison with stable COPD patients,[50,208] but mRNAs for IL-4 and IL-5 were not changed during COPD exacerbations compared to stable disease.[50,55] Severe exacerbations of COPD are associated with increased neutrophilia and upregulation of epithelial mRNA for CXCL5 (epithelial neutrophil-activating peptide 78), CXCL8 (IL-8), CXCR1, and CXCR-2 in comparison with stable disease.[209] Systemic inflammation is now increasingly recognized as a feature of COPD, and increased serum levels of IL-6 during COPD exacerbations have been described.[210]

Bacterial and virus infection can synergistically interact to increase the severity of inflammatory response. Indeed, it has been shown that rhinovirus and *H. influenzae* coinfection at COPD exacerbations is associated with increased levels of serum IL-6 compared with those exacerbations without both pathogens.[211] Similarly, levels of endothelin 1, a potent vasoconstrictor and bronchoconstrictor peptide with important proinflammatory activities in the airways, tend to be higher during COPD exacerbation associated with viral or chlamydial infection, both in sputum and in plasma.[212] Virus-induced COPD exacerbations are also associated with increased plasma levels of IL-10, IL-12, and IL-15,[213] whereas all COPD exacerbations (with or without respiratory virus isolation) are characterized by increased plasma levels of IL-2, IL-13, and vascular endothelial growth factor.[213]

Plasma levels of IL-21, a cytokine important for B-cell development and antibody synthesis,[214] are decreased during COPD exacerbations compared with stable COPD patients, but without statistically significant association between IL-21 levels and antiviral capsid protein (VP1) of rhinovirus IgG_1 antibody concentrations that have shown cross-neutralizing activity across different rhinovirus strains.[215,216] This deficient synthesis of IL-21 might be linked to the susceptibility to COPD exacerbations via other mechanisms, eg, IL-21 is also critical for CD8 T-cell memory.[217]

Plasma levels of IL-19 and IL-22 have been shown to be decreased during COPD exacerbations.[218] IL-19, a proinflammatory cytokine, belongs to the IL-10 family, and is expressed in epithelial cells, endothelial cells, and macrophages.[219] Plasma adiponectin concentrations increase during COPD exacerbations and return to baseline several days to weeks later; the clinical relevance of this is unknown.[220]

Although many cytokines are potentially involved both at the lung level and in terms of systemic inflammation, there has only been one study of anticytokine therapy with the TNFα blocker etanercept for COPD exacerbations.[186]

Inhibiting cytokines in COPD: current knowledge and future strategies

There is clear evidence for a heightened inflammatory response in COPD associated with enhanced expression of a number of key cytokines. Although many of these have been proposed to play a role in COPD pathophysiology, there have been very few trials of agents that block cytokines, usually with blocking antibody approaches. And yet inhibiting cytokines looks like a most promising way of inhibiting the inflammatory process that is likely to underpin the progressive nature of this disease. So far, clinical experience has been mainly limited to the use of anti-TNFα and anti-CXCL8 (IL-8), where the effects observed have not been encouraging. The lack of effect of an anti-TNFα approach in COPD is in stark contrast to the positive beneficial effect of this approach in rheumatoid arthritis. This particular experience would beg the question as to whether blocking of the other cytokines listed earlier would be of ultimate benefit in the treatment of COPD.

Just because the levels of a cytokine or chemokine are elevated in COPD does not mean that suppressing its actions will necessarily be effective as an anti-inflammatory therapy. For example, although the levels of TNFα and CXCL8 are both elevated in COPD, and anticytokine approaches proved effective in animal models of disease, inhibiting these mediators has not been effective in clinical trials of COPD patients. Indeed, despite TNFα levels being increased in COPD patient sputum and serum and it being known as a major driver of the inflammatory response, 6 months' treatment with infliximab showed no clinical benefit, with increased risk of lung cancer and pneumonia being observed.[185] CXCL8 is chemotactic for neutrophils and monocytes, and its levels are increased in COPD; however, treatment with an anti-CXCL8 antibody was ineffective in COPD, and despite early optimism, more than one CXCR2 antagonist has not proved effective in large clinical trials either.[110,111] Furthermore, canakinumab, an anti-IL-1β-specific antibody, has no clinical efficacy in COPD either. As listed earlier, other drugs in development include antibodies directed against IL-5 (mepolizumab), IL-6 (eg, tocilizumab), IL-17 (eg, ixekizumab, brodalumab, and ustekinumab), IL-18, IL-22, IL-23, IL-33, TSLP, and GM-CSF. Studies in mouse models may predict the clinical success of inhibiting these cytokines selectively, but it is only going to be possible to determine whether this approach will work by trying these approaches in COPD itself. Compared with chemokines, the functional redundancy between different cytokines in the pathogenesis of COPD is much less clear, but need for targeting groups of cytokines cannot be excluded.

One potential area that may improve success of anticytokine therapies is in the careful selection of patients with COPD for these clinical trial studies of specific antimonoclonal antibodies. COPD is a mixture of various diseases with distinct phenotypes independent of genetic background.[221] The clinical manifestations of COPD are highly variable between patients, and the level of chronic airflow obstruction is not enough to encompass the diversity of presentation of COPD.[222] Other clinical aspects of COPD that contribute to this diversity include the degree of pulmonary emphysema and chronic bronchitis and the frequency of exacerbations. While defining clinical phenotypes of COPD to link with disease outcomes is an important outcome of this exercise for both the clinician and patient, it is as important to link clinical phenotype to the pathophysiological mechanisms that have been delineated so far for COPD. Therefore, the identification of the inflammatory biomarkers CRP, IL-6, CXCL8, fibrinogen, and TNFα linked to mortality indicates the potential importance of these cytokines as targets for COPD treatment. In addition, the COPD patient with evidence of eosinophilic biomarkers either in blood or sputum may respond to eosinophil-targeted cytokines, such as anti-IL-5 antibody, as has been demonstrated in asthma patients with evidence of eosinophilic inflammation. At the end of the day, it should be possible to define specifically the type of inflammation in a particular COPD patient by the expression of key cytokines or chemokines. In addition, it makes sense to target patients with specific anticytokine therapy if there is high expression of that cytokine, and thus direct and indirect biomarkers of abnormal cytokine expression will be needed.

The effects of anti-IL-5 and anti-IL-13 antibodies in severe asthma[223,224] clearly demonstrate the need for both careful patient phenotyping and the need for good biomarkers of patient phenotypes and of drug efficacy, so that patients can be taken off a treatment if it is ineffective to reduce the risk of any possible side effects and to enable a change in drug treatment in an adaptive design clinical study or in real life.

Disclosure

The authors report no conflicts of interest in this work.

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