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Cytokines in chronic respiratory diseases

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Abstract

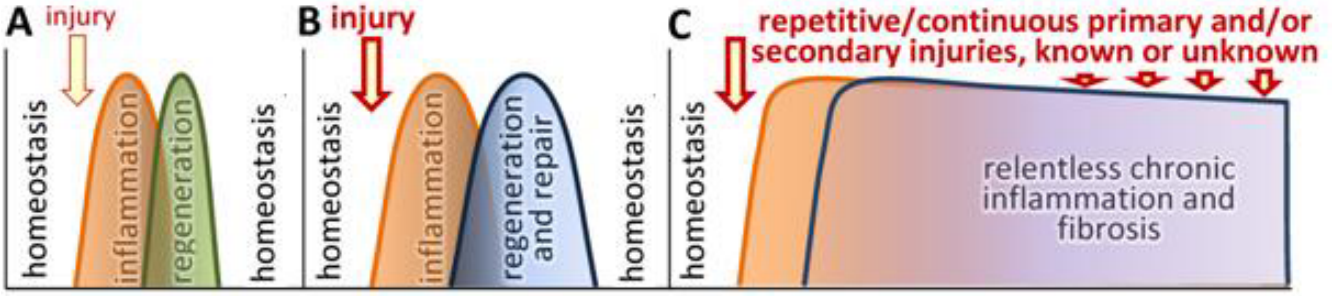
Cytokines are small, secreted proteins that control immune responses. Within the lung, they can control host responses to injuries or infection, resulting in clearance of the insult, repair of lung tissue, and return to homeostasis. Problems can arise when this response is over exuberant and/or cytokine production becomes dysregulated. In such cases, chronic and repeated inflammatory reactions and cytokine production can be established, leading to airway remodeling and fibrosis with unintended, maladaptive consequences. In this report, we describe the cytokines and molecular mechanisms behind the pathology observed in three major chronic diseases of the lung: asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. Overlapping mechanisms are presented as potential sites for therapeutic intervention.

Introduction

The healthy balance of normal processes in the lungs, termed pulmonary homeostasis, can be disturbed by external environmental insults or endogenous factors produced during other diseases. In response to insults, the lung responds with an ancient protective mechanism, inflammation. The subsequent course of events depends on the severity of the injury and on the effectiveness of the inflammatory response (Figure 1). If the injury is mild, structural damage to the lung is limited and the lung tissue will rapidly return to homeostasis (Figure 1a). If the injury is more profound and the structural integrity of the tissue and/or vitality of cells are impaired, then the defect in the tissue will be "patched" with newly formed connective tissue – scar. This repair process substitutes functional components of the tissue with extracellular matrix, which fills the defect and, in most cases, allows for the return to tissue homeostasis (Figure 1b). However, problems arise when the injury is severe or repetitive, and the inflammatory and repair processes fail to limit themselves. Under these circumstances, chronic inflammation and exaggerated repair can ensue, in some cases leading to excessive accumulation of extracellular matrix, or so-called pulmonary fibrosis (Figure 1c). In this brief report, we present the regulation of these processes by key cytokines in three representative chronic diseases of the lung – asthma, COPD, and pulmonary fibrosis.

Cytokines are small, secreted regulatory proteins that play critical roles in immune responses. Cytokines participate in cell-cell communication and regulate many functions including cell survival, cell growth, and induction of gene expression. Cytokines can be produced by many cell types. During the adaptive immune response, CD4+ "Helper T-cells" (TH) produce high levels of cytokines with differing functions. These helper cells can become TH1 cells making high levels of interferon (IFN)γ, TH2 cells making high levels of interleukin (IL)-4, IL-5, and IL-13, or TH17 cells making high levels of IL-17 [1]. These cytokines participate differently in asthma, COPD, and pulmonary fibrosis. While each disease has unique attributes, several cytokines play roles in all three diseases and, thus, may provide interesting targets for therapeutic intervention.

Figure 1. Response of the lung tissue to injury varies depending on the nature of the insult and appropriateness of inflammation and repair



(a) If the injury is mild and structural damage to the tissue is minimal, the process of regeneration allows for a rapid return to homeostasis. (b) A more profound injury affecting the structural integrity of the tissue and vitality of cells leads to repair with deposition of scar tissue, but in most cases there is a return to homeostasis. (c) Repetitive injury, primary or secondary, combined with disturbed tissue responses may lead to continuous inflammation and exaggerated repair, resulting in fibrosis. Note the central involvement of inflammation in all cases, as a bridge between the immediate response to injury and the subsequent repair processes. Although there is a certain overall directionality of the sequence of events from injury to inflammation and to repair, these processes often occur simultaneously at a given time, as indicated by the overlapping corresponding curves.

Asthma

Asthma is a chronic disease of the lung characterized by shortness of breath, wheeze, cough, reduced airflow on expiration, and airway hyperreactivity to non-specific bronchoconstrictors [2]. Recent evidence suggests that asthma is not a single disease, but consists of several subtypes, including allergic and steroid-resistant asthma [3,4]. Allergic asthma is mediated by the TH2 cytokines IL-4, IL-5, and IL-13 (Table 1) [5]. IL-4 participates in the differentiation of naïve CD4+ T cells into the TH2 type and is important for the production of allergen-specific IgE [1]. Furthermore, IL-4 drives the alternative activation of macrophages, which have been shown to increase lung inflammation in mouse models of allergic lung inflammation and to be correlated with asthma severity in asthma patients [6-12]. The role of IL-4 in driving allergic asthma is well known, and recent data suggest that its alternatively spliced variant missing exon 2-encoded region, IL-4δ2, is naturally produced by cells from patients with asthma but not from healthy controls [13]. This splice variant is active independently of wild-type IL-4 and promotes pulmonary inflammation without TH2 skewing [14,15].

Like IL-4, IL-13 can also regulate IgE production and the alternative activation of macrophages because it shares a receptor complex and downstream signaling pathways with IL-4 [16]. Furthermore, IL-13 has a distinct and prominent role in mediating the structural changes observed in the airways by modulating goblet cell differentiation and mucus production, airway smooth muscle cell proliferation, and subepithelial fibrosis [5,17,18]. Such changes lead to airway constriction and hyppereactivity to stimulants, and, after prolonged chronic allergen exposure, tissue remodeling and fibrosis.

IL-5 plays an important role in eosinophilic inflammation during allergic asthma. Studies in both mouse models and human asthmatics have demonstrated that IL-5 is critical for the differentiation of eosinophils from bone marrow precursors and for their trafficking from the bone-marrow

Table 1. Major cytokines involved in pathogeneses of asthma, COPD, and pulmonary fibrosis

Asthma	COPD	Pulmonary Fibrosis
IL-4, IL-5, IL-13	TNF-α, IL-1,	TGF-β, CTGF
IL-25, IL-33, TSLP	IL-6, IL-8, IL-18, IL-32	IL-4, IL-13
IL-17	IL-17	MCP-1, Oncostatin M
TNF-α, IL-1, IL-8, IL-18	TSLP	PDGF, GM-CSF
RANTES, eotaxin	TGF-β	CCL17, PARC/CCL18
GM-CSF, VEGF		SDF-1/CXCL12
		IL-1, IL-17, IL-10

The relative importance of these cytokines is difficult to assess quantitatively; instead, the authors established this order based on their expertise and available literature in the field.
Abbreviations: CCL17, thymus and activation-regulated chemokine (also known as TARC); COPD, chronic, obstructive pulmonary disease; CTGF, connective tissue growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; MCP-1, monocyte chemotactic protein (also known as CCL2); PARC, pulmonary and activation-regulated chemokine (also known as CCL18); PDGF, platelet-derived growth factor; RANTES, regulated and normal T cell expressed and secreted; SDF-1/CXCL12, stromal cell-derived factor-1; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.

to the lung [19-24]. Furthermore, IL-5 enhances eosinophil survival [25]. Thus, the TH2 cytokines IL-4, IL-13, and IL-5 orchestrate the set of physiological responses characteristic of allergic asthma including inflammation, airway hyperactivity, and airway remodeling.

In addition to the classic TH2-cell derived cytokines, cytokines produced by airway epithelial cells have recently been recognized as critical mediators of allergic asthma [26,27]. Airway epithelial cells are the first to encounter inhaled allergens or other agents and are stimulated to secrete IL-25 [28], IL-33 [29], and thymic stromal lymphopoietin (TSLP) [30-33]. IL-25 is produced by airway epithelial cells upon exposure to allergens, particles, and helminths [28,34,35]. IL-33 is present in cells in both full-length and mature forms, of which mature IL-33 is a powerful activator of the TH2 responses [29,36-41], whereas full length IL-33 activates inflammation without engaging the IL-33 receptor component T1/ST2 or engaging the TH2 mechanisms [36]. The IL-33 receptor is critical for development of asthma [42-44]. Both IL-25 and IL-33 stimulate the rapid production of IL-5 and IL-13 by natural helper cells (multipotent progenitor cells, nuocytes, c-Kit+Sca-1+ IL-7R+IL-33R+IL-17RB+ cells) in the airways, which promotes TH2 generation and increases local TH2 cytokine production [45-49]. TSLP primes, polarizes, and maintains TH2 cells [50], and its expression in the airways of patients with asthma has been shown to correlate with disease severity [51-53]. All these TH2-associated cytokines are engaged in an intricate interplay with other cytokines including, but not limited to, TNF-α [54-56], IL-1 [57,58], granulocyte-macrophage colony-stimulating factor (GM-CSF) [57,59,60], vascular endothelial growth factor (VEGF) [61-64], IL-18 [65,66], and IL-17 [67-73]. Based on studies in mouse models, it is believed that TH17 cells and, therefore, IL-17 cytokines play a role in asthma severity by increasing neutrophil recruitment to the airways [74]. Furthermore, the TH17-mediated pathway may contribute to steroid resistance in human asthma, but this has not yet been clearly established [4]. Thus, IL-17-driven asthma may be distinct from allergic asthma and require different therapeutic strategies [3,4]. The chemotactic family of cytokines called chemokines also centrally contributes to pathogenesis of asthma by recruiting specific inflammatory cells into the lung tissue [75-77], including regulated and normal T cell expressed and secreted (RANTES)/ chemokine (c-c motif) ligand (CCL)5 [78-81], eotaxins CCL11, CCL24, and CCL26 [81-84], CXCL8/IL-8 [85,86]. While the TH1 cytokine IFN-γ is typically thought to suppress TH2-mediated responses, several reports indicate that, in certain circumstances, IFN-γ is also involved in promoting disease pathogenesis [87-89].

COPD

COPD is caused by smoking or other prolonged significant exposure to fumes, dust, or polluted air, which causes chronic inflammation of bronchi, destruction of lung tissue (emphysema), and some degree of scarring. The inflammatory process involving T cells, neutrophils, and macrophages is driven by the classical proinflammatory cytokines TNF-α [90,91], IFN-γ [92-94], IL-1 [95], IL-6 [96], IL-8 [90,91,97-102], IL-18 [92,103,104], and IL-32 [105]. Recent evidence also implicates IL-17 in the pathogenesis of COPD [56,92,106-109]. Increased sputum IL-17 levels were identified in COPD patients, and were even more pronounced than those detected in patients with asthma [56]. These levels correlated with a decrease in lung function as measured by a decrease in forced expiratory volume, suggesting a potential role for IL-17 in COPD pathogenesis and defining it as a prognostic target for disease immunotherapy [56]. Although COPD is not considered a TH2 disease, activated TH1 and TH2 cells are found in COPD patients, suggesting that both may contribute to the disease processes. For example, the pro-TH2 cytokine TSLP is expressed and functionally active not only in patients with asthma but also in patients with COPD [33,73]. Similarly, IL-13 may be contributing to mucus metaplasia, airway fibrosis, and vascular remodeling in COPD [92].

Expression of the profibrotic cytokine transforming growth factor (TGF)-β is enhanced in the airways of patients with COPD [110-113]. This appears somewhat counterintuitive because TGF-β is a potent inducer of connective tissue deposition, whereas COPD is characterized predominantly by lung tissue destruction. Nevertheless, pulmonary fibroblasts from these patients respond to stimulation by TGF-β with an enhanced activation of the WNT/β-catenin pathway [114], whereas COPD airway smooth muscles respond to similar stimulation with an enhanced deposition of the proteoglycan perlecan [115], suggesting that TGF-β contributes to architectural changes in the lungs in COPD. Indeed, peribronchial fibrosis does develop in the lungs of patients with COPD, which is in contrast to mostly subepithelial fibrosis in asthma (see above) and interstitial fibrosis in idiopathic pulmonary fibrosis and scleroderma lung disease (see below).

Pulmonary fibrosis

Pulmonary fibrosis – excessive accumulation of scar tissue – develops during the progression of a variety of lung diseases. This process may be self-limiting, but in some cases, the fibrotic process becomes overt and irreversible, leading to a significant decline in lung function, the ability to exchange gas. Pulmonary fibrosis

is the main cause of death in the autoimmune disease scleroderma [116], whereas in patients with idiopathic pulmonary fibrosis, median survival is only two to three years [117]. In cases of such profound pulmonary fibrosis, the available therapies have limited effectiveness. Extracellular matrix, including collagen, accumulates in the lungs through several mechanisms. Resident pulmonary fibroblasts become activated, increase their proliferation rate, while decreasing sensitivity to apoptotic signals, and deposit more extracellular matrix, while slowing down extracellular matrix turnover. Bone marrow-derived cells called fibrocytes home to the lung and differentiate into activated fibroblasts [118-120]. Epithelial-mesenchymal transition, a process by which lung epithelial cells transform into myofibroblasts, also contributes to lung fibrosis [121-123]. All these mechanisms are controlled by cytokines, either through direct recruitment and activation of extracellular matrix-producing cells, or indirectly, through regulation of pulmonary inflammation [124-130], redox balance [131-133], and activity of several enzymatic systems, including matrix metalloproteinases and their inhibitors [130,134-136], and clotting enzymes [126,137-141].

TGF-β is undoubtedly the most potent profibrotic cytokine [142,143]. It is produced in latent form and normally stored as such in tissues in association with extracellular matrix and needs to be activated to exert its functional effect. Thus, TGF-β-driven fibrosis is controlled by the mechanisms of its activation rather than production. In the lungs, activation of TGF-β by αV-containing integrins plays a central role in the mechanism of fibrosis [127,143-146]. Connective tissue growth factor (CTGF) acts in concert with TGF-β, contributing to fibrosis [147,148]. Furthermore, the TH2 cytokines IL-4 and IL-13 are direct activators of fibrosis [149-154], whereas the TH1 cytokine IFN-γ is a potent direct inhibitor of extracellular matrix deposition [155,156]. Interestingly, although the levels of Th2 cytokines are substantially higher in asthma than in fibrotic diseases such as scleroderma or idiopathic pulmonary fibrosis, the severity of fibrosis is higher in the latter diseases. Furthermore, scleroderma lung disease and idiopathic pulmonary fibrosis are characterized by diffuse parenchymal accumulation of extracellular matrix, whereas in asthma, fibrosis is mostly subepithelial. A possible explanation for this paradox is that, in asthma, TH2 cytokines are the predominant drivers of fibrosis, whereas in scleroderma lung disease and idiopathic pulmonary fibrosis, the patients experience a "profibrotic cytokine storm", with elevated levels of all of the cytokines listed in this section. Furthermore, TGF-β is a more potent profibrotic cytokine, exerting its effect at much lower concentrations than IL-4 or IL-13.

The chemokine monocyte chemotactic protein (MCP)-1/CCL2 promotes fibrosis through direct and indirect mechanisms [157-160], as do Oncostatin M [128,161] and platelet derived growth factor (PDGF) [162-164]. An important, predominantly indirect, modulator of fibrosis is the chemokine pulmonary and activation-regulated chemokine (PARC)/CCL18, which is elevated in association with various fibrotic lung diseases, such as scleroderma [165,166], hypersensitivity pneumonitis and idiopathic pulmonary fibrosis [166,167], asthma [168], and sarcoidosis [169]. Although PARC/CCL18 directly activates collagen production in fibroblasts in cell culture [170-173], it exerts its profibrotic action *in vivo* mostly by recruiting profibrotic T cells [127,130,174]. Another chemokine, stromal cell-derived factor (SDF)-1/ chemokine (C-X-C motif) ligand (CXCL) 12, contributes to fibrosis by recruiting bone marrow-derived progenitors of fibroblasts to the lung [175-177]. Numerous other cytokines may contribute to the mechanism of pulmonary fibrosis, but their exact roles remain either controversial or mechanistically unclear, including IL-1β and IL-17 [178-180], IL-10 [181,182], thymus and activation-regulated chemokine (CCL17) [183], and GM-CSF [184-186]. An extensive discussion of cytokines regulating pulmonary fibrosis can be found in [129,187-189].

Cytokine-targeted immunotherapy

The important contribution of cytokines to features of the chronic lung diseases presented above suggests potential targets for therapeutic intervention using blocking antibodies or therapeutic proteins. Indeed, a number of clinical trials have been performed or are ongoing for many of the cytokine targets. The emerging anti-cytokine therapies for asthma are primarily directed toward IL-4, IL-5, or IL-13 [190-195]. Early studies targeting IL-4 met with limited success [195], likely because they did not also block IL-13. More recent studies with blocking anti-IL-13 antibodies or with an IL-4 mutant that blocks the actions of both IL-4 and IL-13 showed greater promise in some, but not all, studies [191-193,195-197]. The varied effectiveness of IL-13-directed therapies is not surprising considering that only 50% of asthmatics show elevated levels of sputum IL-13 [198]. Similarly, there are controversial results on the effectiveness of IL-5 directed therapies [196,197]. While anti-IL-5 antibody was effective at reducing eosinophil numbers in blood and sputum, it was substantially less effective at reducing eosinophil numbers in the lung and had a modest impact on lung function [194]. Therefore, it is clear that currently existing therapies have to be extended to include downregulation of additional pathways that have been shown to play roles in asthma pathogenesis such as TSLP, IL-17, IL-25, IL-33 [199]. Other more

"non-traditional" molecular pathways might also prove to be effective targets. As an example, we recently have shown that neuroimmune semaphorin 4A plays a downregulatory role in experimental asthma severity, in part, by regulation of IL-13 [200,201].

Targets for COPD and lung fibrosis are less numerous. Several drugs targeting the tumor necrosis factor (TNF)-α pathway have been developed and used in clinical settings. Some of them (i.e. mouse/human IgG1 antibody against TNF-β, ifliximab) were found to be effective in asthma but not in COPD [202-205]. A soluble human TNFR2, etanercept, reduced lung pathophysiology in patients with severe forms of disease [54,55]. Clinical studies of a fully humanized IL-1β blocking antibody (canakinumab) and anti-IL-6R blocking antibody (tocilizumab) were reported to be in progress in patients with COPD and rheumatoid arthritis, correspondingly [206], but no final results have been revealed yet. Several drugs have been developed to target the VEGF pathway, which has been implicated in asthma, such as bevacizumab, VEGF-Trap, and PTK737 [207] with clinical trials being limited thus far to cancer, ischemia, and age-related macular degeneration [208]. The identification and targeting of a cytokine active in more than one chronic lung disease would clearly be beneficial.

Summary

There is growing awareness that there are key similarities in the contribution of cytokines and the manifestation of lung pathology among the chronic respiratory diseases [209]. As noted in Table 1, several of the cytokines contribute to multiple chronic disease states (e.g. TGF-β, IL-17, TSLP, IL-4, IL-13). While we have learned much about the general role of cytokines in these diseases, many questions remain unanswered. What is the relationship between the major chronic respiratory diseases? Are there common targets for intervention? Will it be possible in the future to attenuate or even abrogate the undesired excessive responses by therapeutically targeting cytokines? Experiments in animals have been very promising, but their translation into clinical trials lags behind. One difficulty is that cytokines are functionally pleiotropic and redundant, and, as a result, targeting an individual cytokine may have a less than expected effect (due to functional substitution by other, functionally similar, cytokines) or have undesired side effects (due to pleiotropy). Another difficulty is that mouse models do not completely mimic the disease in humans [210-212]. It will be important to further understand these issues to increase the likelihood that targeting cytokines will improve the clinical outcome for patients with chronic lung diseases.

Abbreviations

CCL, chemokine (C-C motif) ligand; COPD, chronic, obstructive pulmonary disease; CTGF, connective tissue growth factor; CXCL, chemokine (C-X-C motif) ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP-1, monocyte chemotactic protein; PARC, pulmonary and activation-regulated chemokine; PDGF, platelet-derived growth factor; RANTES, regulated and normal T cell expressed and secreted; SDF-1, stromal cell-derived factor-1; TGF-β, transforming growth factor beta; TH, T helper cells; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.

Disclosures

The authors declare that they have no disclosures.

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