

Role of Airway Epithelium-Origin Chemokines and their Receptors in COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is characterized with the chronic airway inflammation associated with progressive obstruction of airflow. Airway epithelial cells play an essential role of development in COPD. Chemokines as extracellular signaling proteins have been suggested to be involved in the inflammatory process of COPD. The present review summarized the variation of chemokines in the airway epithelium of COPD patients and discussed the potential roles of chemokines in the pathogenesis of COPD. Increased level of IL-8 was considered as a key and unique chemokine in the initiation and progress of COPD. Others like CXCR3 chemokines and eosinophils-related chemokines should be also considered. Further research will be necessary to explore whether targeting on these chemokines, particularly IL-8 and CXCRs, can be benefit to patients with COPD. It is also important to identify and validate a critical and specific chemokine with differential diagnostic value. The correlation of chemokines with disease severity, diagnosis and therapy in COPD should be further clarified. High-throughout technologies, e.g. genomics, proteomics and bioinformatics, can be more attractive approaches to validate the importance of chemokines in the disease. Although the exact role of chemokines in the pathogenesis of COPD still needs to be explored, anti-chemokines or receptor antagonists may be an alternative of new therapies for patients with COPD.

Keywords: COPD, epithelial cells, chemokines, BALF, sputum.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by a progressive airflow limitation and associated with an abnormal inflammatory response of the lungs to noxious particles or gases [1, 2]. COPD ranks among the top five leading causes of death worldwide and becomes the top three in the mortality by 2020 [3]. Increasing interests in the clinical features and pathogenesis of COPD reflect the worldwide importance of the disease. The over-production of chemokines and activation of chemokines receptors have been suggested to be involved in the abnormalities seen in COPD. These small attractant proteins occur in different stages of the disease and also in several diseases associated with COPD (Fig. 1). Although the potential roles of inflammatory mediators have been well described in asthma [4, 5], little information is known about the production and role of those mediators in COPD.

Bronchoalveolar lavage (BAL) is the most common manner to sample the components of the epithelial lining fluid and determine the protein composition of the pulmonary airways. The recovered BAL fluid (BALF) contains both lung cells and epithelial lining fluid solutes including proteins and inflammatory mediators [6]. Epithelial cells in the human airway are responsible for multiple functions, e.g. absorption, transport, secretion and defense, and can be

activated to produce a number of inflammatory mediators to communicate with other cells and initiate the local inflammatory response. Induced sputum has been suggested as a noninvasive method to study airway secretions, cells and biomarkers, e.g. chemokines [7]. The primary human bronchial epithelial cells (PBECs) *via* biopsies can also provide more precise information about those chemokines. In the present review, we summarize alterations of chemokines recently observed in human airway by different methods, present the potential role of chemokines in the mechanisms and compare the patterns of altered chemokines in COPD with other human airway inflammatory diseases.

CHEMOKINES AND CORRESPONDING RECEPTORS

Chemokines are chemotactic cytokines of 8-10 kDa involved in attracting leukocytes into tissues. Since the first chemokine, interleukin (IL)-8, was described [8, 9], over 50 other chemokines have been recognized to interact with ≥ 17 different receptors [10]. Based on structural homology around four cysteine residues, the chemokine family can be subdivided into four subclasses, -C-, -CC-, -CXC- and -CXXXC-, in which X substitutes for any amino acid. Two subclasses account for most of the chemokines: CXC (α -chemokines) and CC (β -chemokines) chemokines. The CC chemokines are involved in chemoattraction of eosinophil, monocytes and T-lymphocytes.

Of the CXC chemokines, IL-8, growth related oncogene- α (GRO- α) and epithelial-derived neutrophil activator (ENA-78) are of particular interest with their chemoattractant and activating effects on neutrophils. They act through a transmembrane domain-containing seven G-protein-coupled re-

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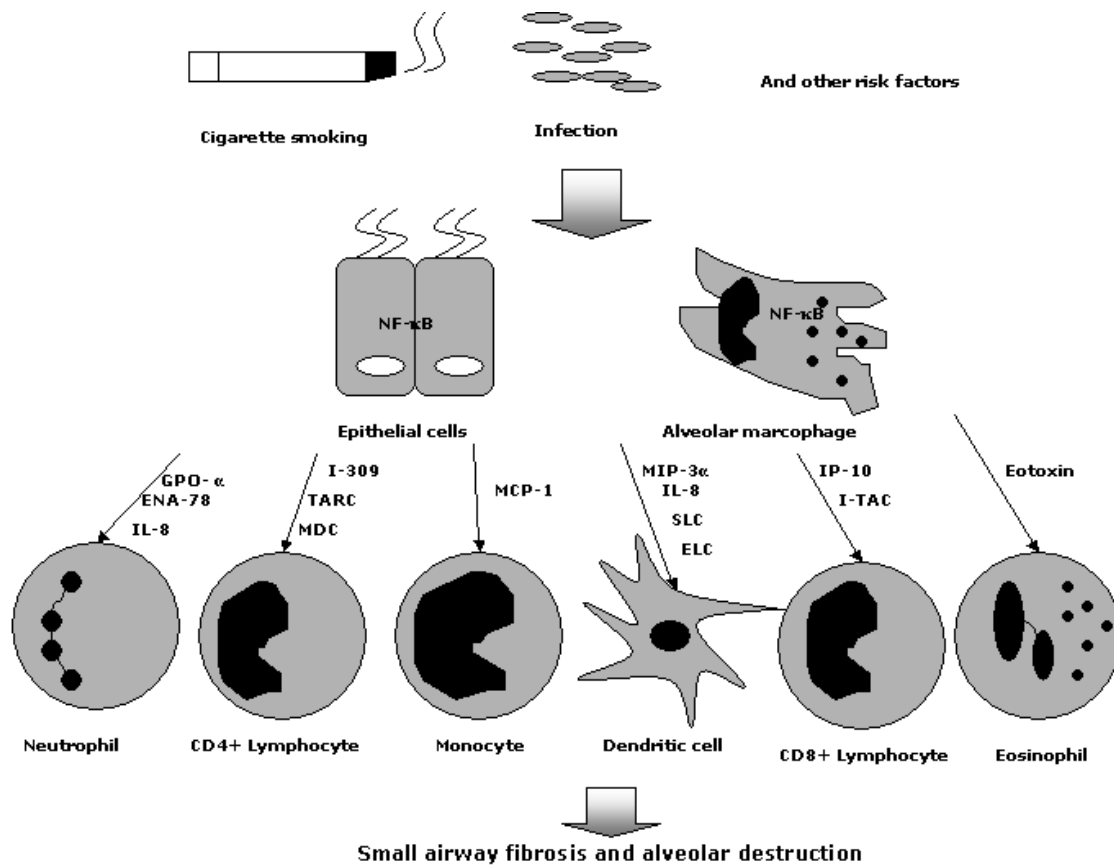


Fig. (1). Schematic illustration of potential mechanism in COPD. Cigarette smoking, infections and other risk factors stimulate airway epithelial cells and alveolar macrophages, leading to activation of the transcription factor nuclear factor ($\text{NF-}\kappa\text{B}$). Then these cells could release various chemokines which can recruit different inflammatory cells by binding corresponding receptors. Chemokine-dominant inflammation may result in the development of small airway fibrosis and alveolar destruction.

ceptor, type 2 CXC receptor (CXCR) 2, whereas IL-8 activates CXCR1. Of the larger family of CC chemokines, normal T-cell expressed and secreted (RANTES), macrophage inflammatory protein 1 α (MIP-1 α), monocyte chemoattractant protein (MCP) 1, 3 and 4, and eotaxin may also play the important role in development of the disease. Eotaxin acting through the type 3 CC receptor (CCR3) is a selective chemoattractant for eosinophils, whereas RANTES exhibits a range of effects on memory T cell, basophils and eosinophils, acting through CCR1, 3 and 5. MCP-3 and 4 may recruit eosinophils and mononuclear cells, whereas MCP-1 can recruit monocytes, lymphocytes and basophils and activate mast cells and basophils. Those ligands and their receptors on airway epithelia obtained from BALF, sputum or biopsies from patients with COPD are listed in Table 1. Of those, IL-8 has been considered to play the critical role in COPD. Although CC chemokines are of great relevance to asthma, the elevation of some chemokines can be also found in COPD.

CXCL8/IL-8 AND ITS RECEPTORS (CXCR1 AND CXCR2)

Increased neutrophils are a feature of airway inflammation in patients with COPD, particularly patients with more severe disease, during exacerbations and with cigarette smoking. CXCL8/IL-8 is the most significant chemokine for

neutrophils, which is produced from endothelial and epithelial cells in the airway. IL-8 acts *via* CXCR1 and 2. CXCR2 protein, but not CXCR1, was expressed by bronchial epithelial cells in COPD patients, mainly in the injured areas [11]. Various inflammatory responses that are of potential relevance in COPD pathophysiology did not affect the transcription regulation and surface expression of CXCR1 and CXCR2 on PBECs [12]. CXCR1 and CXCR2 were found to be significantly upregulated at exacerbations of COPD [13] and proposed to play important roles in mediating IL8-induced chemotaxis of neutrophils [14, 15] and be the target for therapeutic strategies.

The expression of IL-8 protein and mRNA significantly increased in bronchiolar epithelial cells of patients with COPD, in response to several stimuli, including TNF- β , endothelin-1 (ET-1), bacterial products, lipopolysaccharide (LPS), RV infection, TNF- α , oxidative stress and cigarette smoke [16-20]. The secretion of IL-8 was suggested to be regulated transcriptionally by several transcription factors, among which $\text{NF-}\kappa\text{B}$ is predominant [21]. *Via* CXCRs, IL-8 could activate protein kinase B (Akt) and GTPases, leading to enhanced neutrophil adherence to endothelial cells by increasing expression of β_2 -integrins and directing cell migration. Protein kinase B activates phosphoinositide 3 kinase, which then induces F-actin polymerization, resulting in

Table 1. Chemokines Detected in Patients with COPD and other Associated Diseases in Different Samples

Chemokines	Common Name	Corresponding Receptors	Target Cells	Stage	Sputum	BALF	PBECs
CXCL1	GPO- α	CXCR2	N	COPD	(62) \uparrow		(20) \uparrow
CXCL8	IL-8	CXCR2,1	DC,N, Ep	ECOPD	(7, 29, 34, 35, 37) \uparrow	(22, 34) \uparrow	
				COPD	(31, 44, 50, 71) \uparrow	(52, 65) \uparrow	(20, 21, 30, 79) \uparrow
				AATD	(42) \uparrow		
				BHR	(43) \uparrow		
				CS		(38, 52) \uparrow	
CXCL9	Mig	CXCR3	Ep	COPD		(52) \uparrow	
				CS		(52) \uparrow	
CXCL10	IP-10	CXCR3	Th1	COPD		(53) \uparrow	(56) \uparrow
CXCL11	I-TAC	CXCR3	Th1	COPD		(52) \uparrow	
				CS		(52) \uparrow	
CCL2	MCP-1	CCR2	M	COPD	(62) \uparrow	(52, 65) \uparrow	(79) \uparrow
				CB		(67) \uparrow	
				CS		(52) \uparrow	
CCL3	MIP-1 α	CCR5	E	COPD		(63) \uparrow	(79) \uparrow
				CB	(64) \uparrow	(67)x	
CCL4	MIP-1 β	CCR5	E	COPD	(64) \uparrow	(67) \uparrow	
CCL5	RANTES	CCR5	E	COPD	(74) \uparrow	(52, 74, 75), \uparrow	
				CS		(52)	
CCL11	eotoxin	CCR3	E	COPD		(75)low	
				COPD +emphysema		(76) \uparrow	
CCL17	TARC	CCR4,CCR8	Th2	COPD		(53) \uparrow	
CCL20	MIP-3 α	CCR6	DC,N,T	COPD	(80) \uparrow		
CCL22	MDC	CCR4	Th2	COPD		(53) \uparrow	

Abbreviations in Table 1.: Mac, macrophage. En, endothelial cell. DC, dendritic cell. N, neutrophil. T, T lymphocyte. Ep, epithelial cell. ECOPD, exacerbation of COPD. CB, chronic bronchitis. AATD, alpha-1-antitrypsin deficiency. BHR, asymptomatic, nonspecific airway hyperresponsiveness. CS, cigarette smoking. \uparrow , up-regulation. X, undetectable. Sputum, induced sputum samples. BALF, bronchial alveolar lavage fluid. PBECs, primary bronchoepithelial cells obtained from human.

pseudopod formation and chemotaxis [22]. While activating Ras and mitogen-activated protein kinases (MAPK) pathway, IL-8 could also lead to the degranulation in neutrophils. MAPK pathway was suggested to mediate the effect of nicotine through ERK 1/2 and JNK rather than p38 in human bronchial epithelial cells treated with nicotine [23]. These effects could be down-regulated by the intracellular regulator of G-protein signaling proteins by reducing the half-life of the active GTP-bound state of CXCR, leading to reduced IL-8-induced neutrophil migration and adherence [24]. Mucins glycoproteins were overproduced and hypersecreted in COPD, predominantly including MUC5AC and MUC5B in human airway. IL-8 was shown to increase MUC5AC abun-

dance at the posttranscriptional level in lung epithelial cells and normal human bronchial epithelial cells [25], as shown in Fig. (3).

The concentration of IL-8 in the sputum and BALF from patients with COPD was found significantly higher than those with asthma [26-28]. The level of IL-8 varied among different stages of COPD [29]. PBECs and sputum cells from patients with stable COPD show significantly higher release of IL-8 induced by TNF- α , as compared to smokers and healthy controls [20, 21, 30]. The concentration of IL-8 in sputum was closely associated with the degree of airflow obstruction and suggested as a biomarker to evaluate the severity of airway inflammation [31]. Clinically stable,

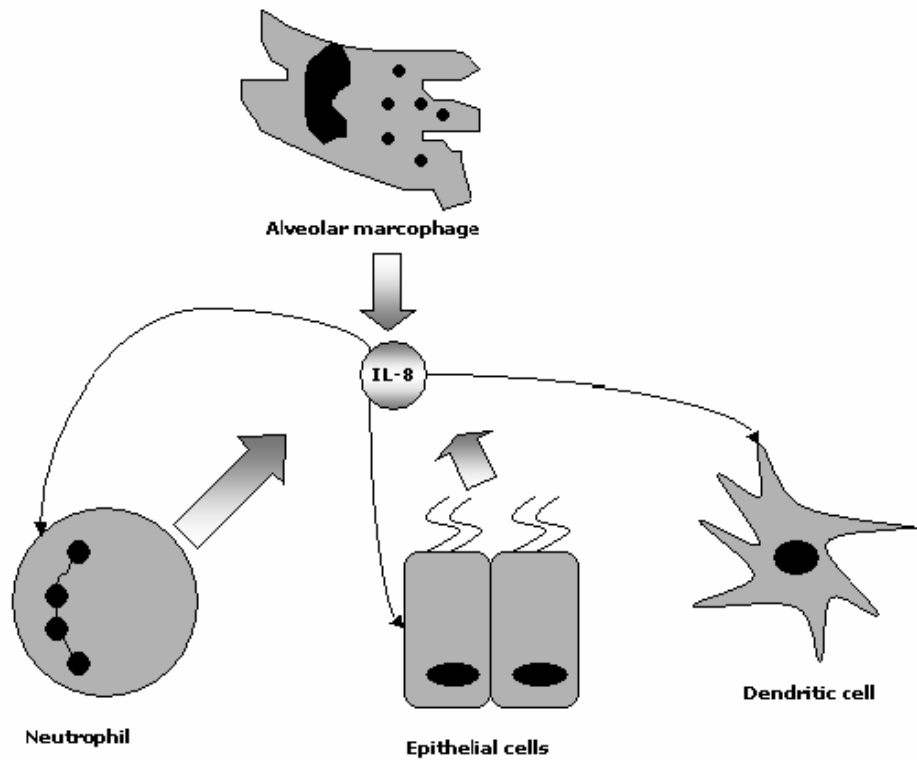


Fig. (2). The role of IL-8 in the inflammation of COPD. IL-8 can be produced by the airway epithelial cells, in addition to neutrophils and macrophages, and then interacts with CXCR1 and CXCR2 on neutrophils, epithelial cells and dendritic cells, leading to different responses.

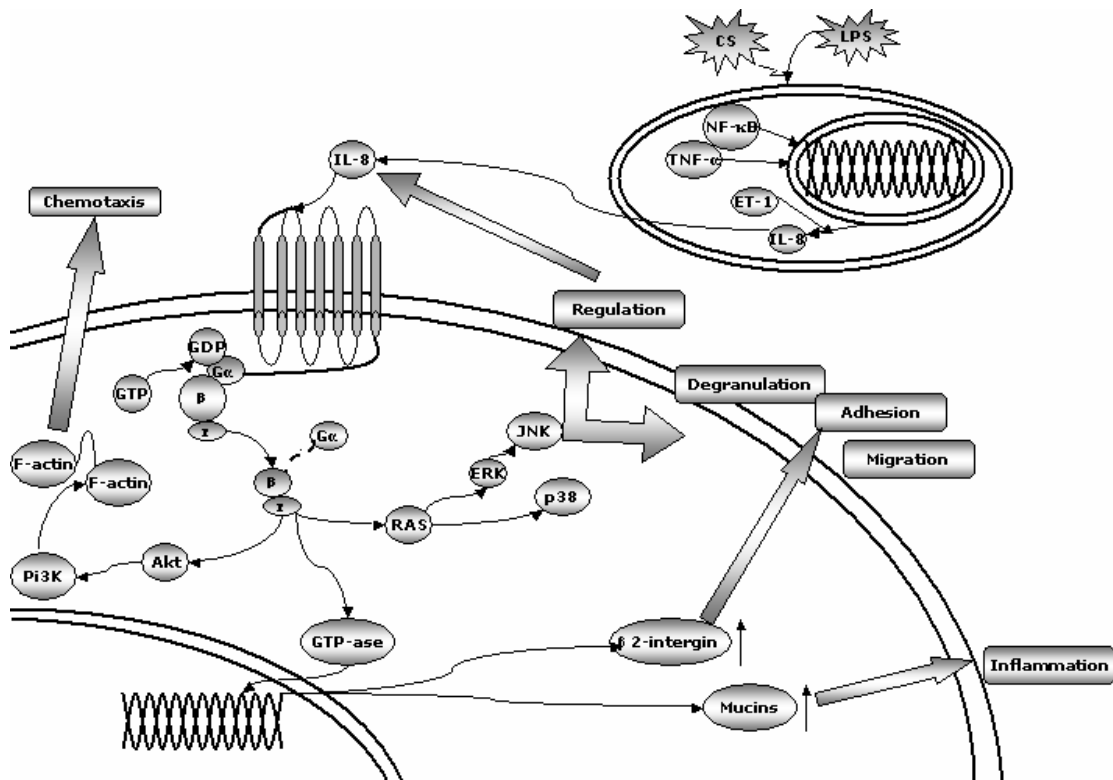


Fig. (3). The regulation of IL-8 in COPD. In response to stimulus, IL-8 could be upregulated in epithelial cells where NF-κB, INF-α and ET-1 may influence the production of IL-8. IL-8 leads to activation of complex signaling pathways and initiates the airway inflammation *via* CXCRs.

moderate COPD was also found to be associated with equally stable IL-8 in sputum [32]. Patients with more frequent exacerbations had the higher baseline of IL-8 in sputum, probably predicting the frequency of exacerbation occurrence [33]. IL-8 levels in BALF from patients with stable COPD had no further increase if exacerbations did not occur [34]. However, IL-8 levels in the sputum and in PBECs increased during exacerbations [13, 34, 35]. Infections are a major trigger of exacerbations of COPD. The sputum levels of IL-8 increased in both viral and bacterial infections along with the detection of pathogen [36, 37].

Cigarette smoking, as a major cause of COPD, was found to be associated with increasing amounts of airway IL-8 [38]. The sputum levels of IL-8 significantly elevated in healthy smokers versus COPD patients with smoking history [39], suggesting ongoing inflammation in airways and circulation of patients with COPD after smoking cessation. The α 1-antiprotease deficiency was found to be associated with COPD [40], while higher level of IL-8 was detected in α 1-antiprotease deficiency patients with or without airflow obstruction [41, 42], similar to stable COPD, supporting the hypothesis of a genetic risk factor for COPD. Likely in asymptomatic, nonspecific airway hyperresponsiveness, the sputum level of IL-8 also increased as compared with control subjects [43], predisposing to development of COPD.

The assessment of airway inflammation and bronchodilator responses could help the selection of specific therapies and the prediction of clinical outcomes for COPD patients [44]. Clinical study demonstrated that long-term treatment with theophylline could reduce airway inflammation in stable COPD patients by decreasing IL-8 level [45]. The production of IL-8 could be reduced by inhaled steroids in both BALF and PBECs [46, 47]. Other antagonists, e.g. theophylline [45], clarithromycin [48], monoclonal antibody against IL-8 [49, 50], could also down-regulate the expression of IL-8 and inhibit neutrophil chemotaxis.

CXCR3 CHEMOKINES

CXCR3 is preferentially expressed on lymphocytes, particularly on type-1 T-lymphocytes. It could also be detected in the S + G(2)/M phases in the cell cycle of human airway epithelial cells [51]. CXCR3 interacts with interferon- γ -inducible protein of 10 kDa (IP-10; CXCL10) and interferon-inducible T cell- α chemoattractant (I-TAC; CXCL11). All three chemokines produced by stimulated bronchial epithelium could be upregulated and found in BALF of COPD patients [52, 53], while CXCL11 might be also regulated by other factors [54]. Upon stimulus, CXCR3 was triggered to express in human airway epithelial cells [55], playing a central role in the trafficking of T lymphocytes from the pulmonary interstitial tissue into both large and peripheral airways during the onset and resolution of pulmonary inflammation [52, 56, 57]. These results may be valuable in designing novel strategies to antagonize CXCR3 mediated immunological reactions and chemotactic effects on T cells.

CD8(+) T lymphocytes release IFN- γ which stimulates airway epithelial cells to produce CXCR3 chemokines, leading to the secondary recruitment of CD8(+) T lymphocytes. The number of CXCR3 (+) cells in the epithelium and submucosa was found to increase in smokers who developed COPD [56]. These patients had a chronic airway inflamma-

tion characterized by an increased infiltration of T-lymphocytes, particularly CD8(+), in the airways and lung parenchyma. Activation of CXCR3 could induce DNA synthesis, cell proliferation and stimulation of MAPK pathways [51]. CXCL11 could stimulate the migration of T lymphocytes between the bronchial epithelia in either direction [58]. IkappaB kinase 2 was involved in the IFN- γ -stimulated release of CXCR3 ligands through a novel mechanism independent NF- κ B [54]. In human airway epithelial cells, CXCR3-mediated chemotaxis was involved by a G protein, which activates both the p38 MAPK and PI3K pathways in a calcium-independent fashion [58].

CXCR2 AND CXCL1

GRO- α /CXCL1 was secreted by alveolar macrophages and airway epithelial cells in response to stimulation of TNF- α and IL-17 in COPD [20, 21, 59, 60]. It could activate neutrophils, monocytes, basophils and T lymphocytes *via* CXCR2 [61]. PBECs from patients with COPD showed significantly higher in TNF- α -induced release of GRO- α compared to those from smokers without airflow limitation [20]. In sputum, the levels of GRO- α and MCP-1 had significantly positive correlation with neutrophil numbers, contributing to the inflammatory load associated with COPD [62].

CC CHEMOKINES AND CORRESPONDING RECEPTORS

CCL2, CCL3 and CCL4

MCP-1/CCL2, MIP-1 α /CCL3 and MIP-1 β /CCL4 are CC-chemokines, as chemoattractants for inflammatory cells like macrophages, lymphocytes and eosinophils. Higher level of CCL3 in BALF was found to be positively correlated with numbers of alveolar macrophages from BALF [63]. This may have relations with the exaggeration of inflammatory process in the airway. The levels of MIP-1 β in sputum from COPD patients were significantly higher than that from the healthy [64]. Higher sputum levels of MCP-1 might be involved in the differentiation of monocytes into macrophages, a role in the pathogenesis of inflammation in COPD [62, 65]. MCP-1 was released from lung epithelial cells in patients with α 1-antiprotease deficiency, perhaps contributing to emphysema [66]. On the contrary, MIP-1 β was found to a potential chemoattractant for eosinophils in patients with chronic bronchitis [64, 67].

CCR5

CD8+ T cells are considered as the key player in the pathogenesis of COPD. Loss of lung function in patients with COPD was associated with a high percentage of CD4+ and CD8+ T lymphocytes expressing CCR5 and CXCR3 [52, 68, 69]. However severe COPD is characterized by lower numbers of CD3+ and CD8+ cells and CD3+ cells coexpressing CXCR3 and CCR5. T lymphocyte infiltration was inversely correlated with the degree of airflow limitation [70]. These findings are consistent with systemic inflammation in COPD associated with an increased influx of cytotoxic and Th1 cells into the airway.

Eosinophil-Selective Chemokines

While neutrophils and IL-8 may have a great influence on nonreversible obstructive airways, eosinophilic inflammation may play a substantial role in COPD [44]. Eosinophils

increased in COPD airways and lungs, although they were not considered as the predominant inflammatory cells as they are in asthma. There was a small increase of eosinophils and eosinophil basic proteins in sputum and BALF from patients with COPD or exacerbations of chronic bronchitis [38, 71, 72]. RANTES/CCL5 could activate CCR3 and was strongly expressed in airway epithelial cells in COPD and CB exacerbation [73]. The levels of CCL5 in BALF and sputum of smokers were higher than nonsmokers [52, 74, 75], suggesting a potential role for CCL5-CCR3 signaling in COPD. Although studies have found an elevated level of CCL11 in BALF [76], the levels of CCL11 in sputum was much higher in asthma than COPD [27]. These investigations reveals that CCL11 may not have prominent function in COPD as it in asthma. It is still questionable that the over-expression of CCR4 exists in asthma and COPD [77].

COMPARISON WITH ASTHMA

Both asthma and COPD have chronic airway inflammation. Severe asthma shares similar clinical phenomena with COPD. However, the difference in inflammatory cells with different patterns of chemokines may be one of the most important factors between two diseases. Studies demonstrated an increased proportion of eosinophils in asthmatic BALF, whereas more neutrophils were observed in COPD. The production of IL-8 in the airway, e.g. sputum and BALF, in patients with COPD was higher than those in asthmatics [28, 65, 71, 77, 78]. The evaluation of BALF reveals more differences in biochemical features of airways inflammation in two diseases than that of induced sputum [28]. In contrast to IL-8, the expression of several T cells attracting chemokines, such as CXCL10, CCL17 and CCL22, in the epithelium was not significantly different between asthma and COPD, but significantly higher than nonsmokers [53]. This may indicate the potential common pathological mechanisms of asthma and COPD.

SUMMARY AND FUTURE INDICATION

Many chemokines may contribute to the pathogenesis of chronic inflammation and structural changes in COPD. The airway epithelial cells act the primary player to produce chemokines, in addition to activated inflammatory cells, such as alveolar macrophages, neutrophils and T lymphocytes. The airway epithelium-produced chemokines in COPD patients may be involved in the pathological injury and dysfunction of the lungs. The recruitment of neutrophils by IL-8 has been recognized as a key and unique role in the initiation and progress of COPD. Others like CXCR3 chemokines and eosinophils-related chemokines should be also considered. Further research will be necessary to explore whether targeting on these chemokines, particularly IL-8 and CXCRs, can be benefit to patients with COPD. It is also important to identify and validate a critical and specific chemokine with differential diagnostic value. The correlation of chemokines with disease severity, diagnosis and therapy in COPD should be further clarified. High-throughout technologies, e.g. genomics, proteomics and bioinformatics, can be more attractive approaches to validate the importance of chemokines in the disease. Although the exact role of chemokines in the pathogenesis of COPD still needs to be explored, anti-chemokines or receptor antagonists may be an alternative of new therapies for patients with COPD.

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