Cytokines and Therapy in COPD* : A Promising Combination?

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A Promising Combination?

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COPD is a major health problem, with patients showing a progressively declining, largely irreversible, change in lung function. This is associated with chronic airways inflammation and structural remodeling, including loss of alveolar walls, and goblet cell metaplasia with mucus hypersecretion. Inflammatory cells may contribute to the airway remodeling via secretion of proteases, fibrotic or mitogenic growth factors, and cytokines. In turn, airway remodeling may contribute to the clinical symptoms of COPD. Currently available therapies are directed to improvement of clinical symptoms and reduction of the airways inflammation. The commonly used glucocorticosteroids are expected to reduce the inflammation by acting on kinases or transcription factors necessary for expression of pro-inflammatory cytokines or chemokines. However, several long-term and short-term studies showed that glucocorticosteroids are rather ineffective in improving lung function and reducing the airway inflammation in patients with COPD. New therapeutic strategies may reduce the inflammation and alleviate the clinical symptoms of COPD. Tumor necrosis factor-α, interleukin-8, and monocyte chemoattractant protein-1 are important chemotactic proteins for macrophages and neutrophils, the predominant inflammatory cells associated with COPD. As lung levels of these cytokines are higher in COPD compared to non-COPD patients, they may represent targets for novel therapies. ***(CHEST 2002; 121:209S–218S)***

Key words: antagonists; chemokines; COPD; cytokines; interleukin-8; monocyte chemoattractant protein-1; receptors; therapy; tumor necrosis factor

Abbreviations: GRO = growth-regulated oncogene; IFN = interferon; IL = interleukin; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; MMP = matrix metalloproteinase; SLPI = secretory leukocyte proteinase inhibitor; TNF = tumor necrosis factor; TNFR = tumor necrosis factor receptor

COPD is a major health problem, ranking among the most common causes of death in Western societies. It is defined by a progressive declining lung function that is only partly reversible by bronchodilator drugs. Although epidemiologic studies demonstrated a close association with cigarette smoking, only 10 to 20% of smokers develop COPD. The disease can be subdivided into three distinct pulmonary disorders: chronic bronchitis, small airway disease (bronchiolitis), and emphysema, which show different features such as goblet cell metaplasia and mucus hypersecretion in chronic bronchitis, and destruction of alveolar septae in emphysema.[1] It has been recognized that COPD is characterized by chronic inflammation in the airways or alveoli that differs from that seen in asthma, involving increased numbers of neutrophils, macrophages, CD8+ T cells, and/or mast cells in the airway walls, alveolar compartments, and vascular smooth muscle.[2–10] In a subpopulation of COPD patients with chronic bronchitis, the obstruction seems to be partially reversible and is accompanied by the presence of airway eosinophils.[11–14] Activation of inflammatory cells is thought to be involved in the airway and alveolar remodeling. For example, neutrophils and eosinophils possess granules containing matrix-degrading proteases. Activated neutrophils also produce reactive oxygen free radicals such as H_2O_2. Proteases and free radicals can damage the epithelium and underlying basement membrane. This is normally followed by a repair process that includes the secretion of antiproteases, such as secretory leukocyte proteinase inhibitor (SLPI) and tissue inhibitor of metalloproteinases by epithelial cells in order to regulate the proteolytic processes.[15] Activated macrophages, T cells, and mast cells also produce and secrete matrix metalloproteinases (MMPs) that can damage the epithelial barrier. The repair process is thought to be disturbed in COPD due to an imbalance in the protease-antiprotease balance.[16,17] Hence, inflammatory cells may be directly involved in airway wall remodeling.

Cytokines and Chemokines

Migration and activation of inflammatory cells is regulated by cytokines and chemokines, small proteins secreted by a variety of structural cells, such as epithelial, endothelial, smooth muscle, and fibroblasts, as well as by inflammatory cells. Cytokines associated with COPD include tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and interleukin (IL)-1β and IL-6.[2,18–20] The chemokines are chemotactic cytokines showing 2, 4, or 6 conserved cysteine residues. Based on the number and spacing of conserved cysteines, chemokines are assigned to four families: α- (CXC), β- (CC), CXXXC, and C chemokines in which X denotes the number of noncysteine residues between the first two conserved cysteines. At least 28 CC, 15 CXC, 2 XC, and 1 CX_3C chemokines have been described (Table 1).[21] Cytokines and chemokines act via binding to one or more cellular transmembrane receptors. For TNF-α, this includes TNF-α receptors (TNFRs) 1 (TNFR p55) and 2 (TNFR p75). For mammalian chemokines, a summary of the seven-transmembrane, G protein-coupled receptors is provided in Table 2.[22] The Duffy and D6 chemokine receptors are not shown as they bind chemokines in a nonspecific manner, and do not transduce intracellular signals. Significant redundancy is observed for several chemokines with respect to receptor binding. That is, in some cases, one receptor subtype can bind several chemokines, whereas a given chemokine can bind to several receptor subtypes (Table 1). Thus, if one

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Table 1—*Overview of Expression of Chemokines in Human Lung

Old Names	New Names	Main Receptors	Cellular/Tissue Expression
CC			
6Ckine	CCL21	CCR7/CCR10	Human lymph nodes, mouse lung
Eotaxin-1	CCL11	CCR3	**Mφ, Eos, Epi, F**, EC
Eotaxin-2	CCL24	CCR3	**Epi,** Mφ, T
Eotaxin-3	CCL26	CCR3	**Epi,** EC
HCC-2	CCL15	CCR1/CCR3	**Lung leukocytes**
I-309	CCL1	CCR8	T, MC
MCP-1	CCL2	CCR2	**Mφ, MC, Epi, EC, SM, F**
MCP-2	CCL8	CCR2/CCR3	**SM,** F
MCP-3	CCL7	CCR1–3	**SM,** Mφ, MC, F
MCP-4	CCL13	CCR2/CCR3	**Epi, SM**
MDC	CCL22	CCR4	**Mφ, Epi,** DC, T
MIP-1α	CCL3	CCR1/CCR5	**Mφ, PMN, Epi, F, SM,** T, Eos
MIP-1β	CCL4	CCR5	**Mφ, PMN, Epi, F, SM,** T, MC
MIP-3α	CCL20	CCR6	**Mφ, T, EC; F**
MIP-3β	CCL19	CCR7/CCR11	Lymph nodes
PARC/DC-CK1	CCL18	?	**Mφ, DC**
RANTES	CCL5	CCR1/CCR3/CCR5	**Mφ, T, Eos, Epi, F, SM**
TARC	CCL17	CCR4	**Epi**
CXC			
ENA-78	CXCL5	CXCR2	**Mφ, Epi, EC, SM**
GCP-2	CXCL6	CXCR1/CXCR2	EC
GRO-α	CXCL1	CXCR2/CXCR1	**Mφ, Epi,** EC
GRO-β	CXCL2	CXCR2	**Mφ, Epi,** MC
GRO-γ	CXCL3	CXCR2	**Mφ, Epi,** MC
IL-8	CXCL8	CXCR1/CXCR2	**T, PMN, Mφ, Epi, EC, F, SM,** Eos
IP-10	CXCL10	CXCR3	**Mφ, Epi,** PMN, EC, F
I-TAC	CXCL11	CXCR3	**Epi,** Mφ, PMN
Mig	CXCL9	CXCR3	**Epi, Mφ,** PMN
SDF-1	CXCL12	CXCR4	**Epi, F**
C			
Lymphotactin-α	XCL1	XCR1	**Lung,** T
Lymphotactin-β	XCL2	XCR1	**Lung,** T
CX3C			
Fractalkine	CX3CL1	CX3CR1	**EC,** T, DC, Epi

*Chemokines are shown using their former and new names, and are grouped according to their amino acid sequences. Major receptors are also shown, as well as the cell types expressing them. Chemokines and their producing cell types in the lung are shown in bold. T = T cell; PMN = neutrophil; Mφ = macrophage; MC = mast cell; Eos = eosinophil; Epi = epithelial cell; EC = endothelial cell; F = fibroblast; SM = smooth muscle; DC = dendritic cell; ? = unknown; RANTES = regulated on activation, normal T-cell expressed and secreted; TARC = thymus and activation regulated chemokine; MDC = macrophage-derived chemokine; PARC = pulmonary and activation regulated chemokine; I-TAC = IFN-γ-inducible T-cell α chemoattractant; IP-10 = IFN-inducible protein 10; SDF-1 = stromal cell derived factor 1; HCC-2 = human cell cycle 2; ENA-78 = epithelial neutrophil activating protein; GCP-2 = granulocyte chemotactic protein 2; Mig = mouse monokine induced by IFN-γ.

chemokine or receptor is inactivated, its effector function(s) may be replaced by others. As discussed later, however, expression of some chemokine and cytokine receptors is cell specific, often resulting in cell type-specific effects.

Glucocorticosteroid Therapy in COPD

According to the recent guidelines for COPD,[23] regular clinical treatment of COPD includes the use of bronchodilators (β_2-adrenoceptor agonists, anticholinergic drugs, and methylxanthines such as theophylline), and oral or inhaled corticosteroids. Alternative therapies currently being explored include phosphodiesterase 4 inhibitors, leukotriene receptor antagonists, and inhibitors of 5-lipoxygenase and cyclooxygenase. More specific details on some of these agents are provided, respectively, by Sturton and Fitzgerald, and Kilfeather in this supplement. Such treatments are normally expected to improve the quality of life by (subjective) improvement of lung function, dyspnea, and reduced inflammation. Studies[24–28] *in vitro* have shown that corticosteroids reduce inflammatory responses by intracellular inhibition of transcription or translation of pro-inflammatory cytokines and chemokines. Hence, corticosteroid therapy may inhibit the increased expression of TNF-α, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, and IL-8 observed in COPD.[7,19,29,30]

In contrast to the positive effects in asthmatics and a subpopulation of patients with COPD, *ie*, those with bronchial hyperresponsiveness and eosinophilia, regular

Table 2—*Chemokine Receptor Distribution

Chemokine Receptors	Cell/Tissue
CCR	
CCR1	**Mφ,** Eos, DC, T
CCR2	**Mφ, MC,** DC, T, NK, Epi, F, EC
CCR3	**Eos, Epi, F,** MC, T
CCR4	**T,** NK, DC
CCR5	**Mφ, T,** NK, DC
CCR6	T, DC
CCR7	T, NK, DC, B
CCR8	Mφ, T
CCR9	Mφ
CCR10	**Trachea,** T, DC, EC, F
CCR11	**Epi, lung**
CXCR	
CXCR1	**PMN, Mφ,** MC, DC
CXCR2	**PMN, Mφ,** Epi, EC
CXCR3	**T,** NK
CXCR4	**T, Mφ, DC, Epi, EC,** B
CXCR5	B
XCR	
CR1	T
CX3CR	
CX3CR1	Mφ, T, NK

*The receptors are grouped according to their ligand binding into CCR, CXCR, XCR, and CX3CR. Receptors expressed in human lungs as well as cell types expressing them are shown in bold. B = B cell; NK = natural killer cell; see Table 1 for expansion of other abbreviations.

corticosteroid treatment of patients with COPD has been disappointing. Some studies[31–33] showed that long-term therapy with inhaled corticosteroids leads to an improvement in FEV_1 only during the first 3 to 6 months of treatment, whereas after that period, the FEV_1 declines at the same rate as in the placebo-treated subjects. Another study[34] did not show any improvement in FEV_1. Short-term treatment (2 to 4 weeks) with corticosteroids does not seem to affect the airways inflammation (numbers of neutrophils, macrophages, lymphocytes, eosinophils) or expression of cytokines (TNF-α, IL-8) and antiproteases (SLPI, tissue inhibitor of metalloproteinases) in patients with COPD.[19,35] Corticosteroids may also cause adverse effects such as bone fractures due to loss of bone or inhibition of bone mineralization, impaired wound healing, increased bruising, and loss of extracellular matrix.[32,36–38] Given the rather ineffectiveness of corticosteroid treatment in COPD, and the risk of adverse effects, more specific therapies directed against the reduction of inflammation are desirable.

Cytokines and Possibilities for New Therapies

Neutrophils and macrophages are the predominant inflammatory cells in COPD tissue, BAL fluid, and sputum. Although they can play crucial roles in microbicidal host defense, both of these cell types also cause significant detrimental effects by causing airway wall damage and remodeling via, for example, the actions of secreted proteases.[17,26,39,40] Important chemotactic and activating cytokines for these inflammatory cells include TNF-α, IL-8, MCP-1, and MIP-1α, whose expression levels have been demonstrated to increase in sputum,[19] BAL fluid,[29] plasma,[41] or lung tissues[7,30] from patients with COPD. Also, increased numbers of IFN-γ-positive T cells in peripheral blood were reported in patients with COPD.[18] Although many cytokines, chemokines, and arachidonic acid metabolites may be involved in neutrophil and monocyte/macrophage effector functions, some studies suggest that TNF-α, IL-8, MCP-1, and MIP-1α, in particular, play important roles in this regard. These proteins, therefore, are the primary focus in ensuing sections.

TNF-α- and TNFR-Based Therapies

Studies have shown that TNF-α expression levels in patients with COPD may be higher, due either to induction by *eg*, cigarette smoking or genetic aberrations. For example, TNF-α is secreted by cultured bronchial epithelial cells on exposure to cigarette smoke or its condensate.[42] Alternatively, other studies reported the presence of gene-activating TNF-α polymorphism in patients with COPD,[43–45] resulting in a constitutive higher expression of TNF-α.[46] TNF-α has multiple pro-inflammatory actions, including neutrophil degranulation accompanied by release of proteolytic enzymes like lysozyme and stimulation of the respiratory burst[47–49] (Fig 1).

In addition to its pro-inflammatory actions, TNF-α has also been reported to have direct effects on epithelial cells. TNF-α is capable of inducing airway mucous cell metaplasia and hypersecretion *in vitro* and *in vivo*, features reminiscent of the goblet cell metaplasia observed in chronic bronchitis.[50,51] Other effects include decreased interepithelial binding and cell death *in vitro*,[52,53] emphysematous lesions and alveolar collagen deposition in murine alveolar walls,[54,55] induction of IL-1, TNF-α, IL-8, and MCP-4 expression,[56–59] and of IFN-γ receptors on epithelial cells.[60] IFN-γ in turn inhibits the proliferation and decreases desmosome formation of epithelial cells[53] and may, therefore, be involved in destruction of epithelial integrity and formation of emphysematous lesions. Targeted overexpression of IFN-γ in type II pneumocytes in mice resulted in emphysema, higher numbers of activated pulmonary neutrophils and macrophages, in addition to increased activity of MMP-9 and MMP-12. Antiprotease SLPI levels were decreased.[61] Such data indicate that TNF-α has direct and indirect (via IFN-γ) effects on epithelial barrier functions, *eg*, via inducing cell death and emphysema, and clearance function (replacement of ciliated cells by goblet cells), and may contribute to the clinical deterioration seen in COPD. The induced pro-inflammatory cytokine expression and protease release can perpetuate the inflammatory cell influx and activation, causing distortion of the airways architecture. Anti-TNF-α or anti-TNFR therapies may, therefore, provide more specific means to impair inflammation and epithelial remodeling.

Studies *in vivo* in mice and humans have revealed that TNF-α is involved in the recruitment of macrophages to sites of inflammation. Thus, in chronic colitis (Crohn's

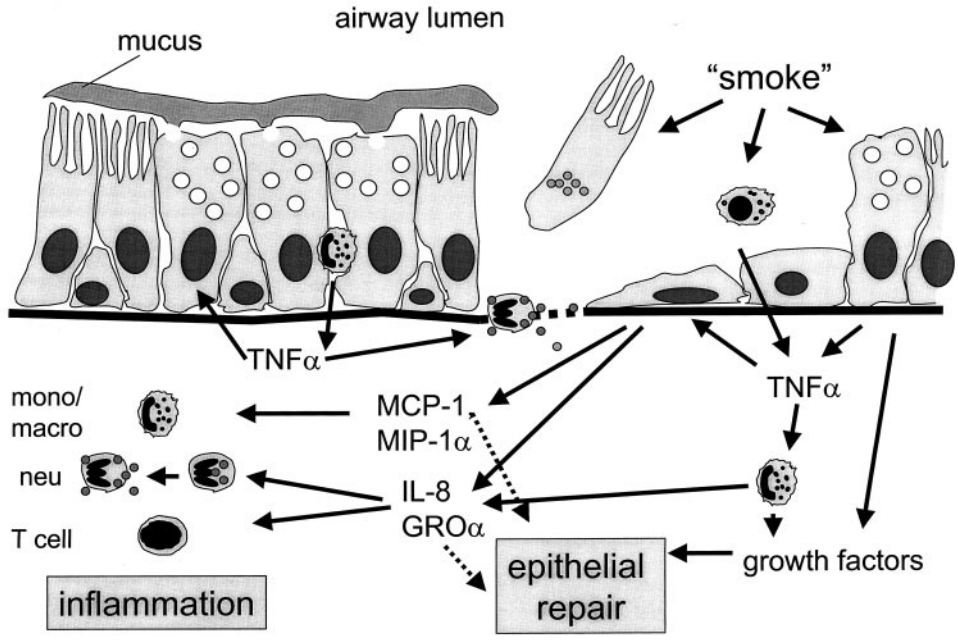

FIGURE 1. Simplified scheme of cytokine and chemokine actions in human lungs. On triggering, *eg*, with cigarette smoke, epithelial cells are damaged, and tissue or alveolar macrophages and epithelial cells produce TNF-α. In turn, TNF-α stimulates migration of monocytes/macrophages and neutrophils to the airway epithelium. Macrophages and epithelial cells are induced to produce IL-8, GRO-α, MCP-1, and MIP-1α. IL-8 and GRO-α also stimulate migration of neutrophils and T cells to the airway epithelium. Both TNF-α and IL-8/GRO-α cause degranulation of neutrophils and respiratory burst with production and release of free radicals that cause matrix and epithelial damage. MCP-1 and MIP-1 stimulate the influx of monocytes/macrophages. Alternatively, TNF-α can also cause epithelial damage and death, goblet cell metaplasia, and/or mucus hypersecretion. TNF-α can also stimulate expression of epidermal growth factors that orchestrate epithelial repair. IL-8/GRO-α and MCP-1 may be directly involved in epithelial repair. mono = monocyte; neu = neutrophil; macro = macrophage.

disease) and rheumatoid arthritis, diseases characterized by the presence of macrophages, T cells, and neutrophils,[62,63] therapy with neutralizing antibodies directed against TNF-α reduces the inflammation, whereas clinically the patients improved, showing reduced symptoms and an improved quality of life.[64–68] In addition, in Crohn's disease, > 30% of the fistulae closed.[67] The infiltration of macrophages as well as the expression of IL-8 and MCP-1 were also reduced in patients with rheumatoid arthritis after a single dose of anti-TNF-α.[65] Similar effects were seen in animals and patients treated with a chimeric ligand-binding domain of TNFR p75 linked to the Fc portion of human IgG1. With regard to chronic lung diseases, clinical trials have begun, including a phase II trial with the TNFR-Fc chimera in patients with atopic asthma, at the National Heart, Lung, and Blood Institute, Bethesda, MD.

As a caution, however, anti-TNF-α treatment may be disadvantageous in some conditions such as endotoxinemia or sepsis.[69,70] For example, following a single dose of anti-TNF-α, plasma levels of IL-1, IL-6, and IL-8 were not reduced in patients with severe sepsis, whereas TNF-α levels were only reduced transiently.[69] Also, the clinical aspects of sepsis were not affected by this treatment. Anti-TNF-α treatment of chimpanzees that were injected with endotoxin reduced TNF-α and IL-8 levels but did not impair neutrophilia and lymphopenia, indicating that TNF-α is not a key regulator for neutrophilic inflammation in this model. As COPD patients are prone to bacterial infections, therapy with anti-TNF-α or TNFR-Fc during infectious exacerbations may have only limited effectiveness. To date, few side effects of the anti-TNF-α therapies are reported, including local reactions at the injection site, hypersensitivity reactions, and minor upper airway infections. Minor events include aplastic anemia and demyelination syndrome by TNFR-Fc.[63,67,68] Support for demyelination syndrome was provided by Liu et al,[71] where mice lacking TNF-α were more susceptible to neurologic changes and inflammation than their wild-type counterparts.

CXC Chemokine and CXCR-Based Therapy

IL-8 and growth-regulated oncogene (GRO)-α are expressed by lung epithelium, fibroblasts, endothelial cells, and alveolar macrophages, and their expression can be induced by stimuli such as cigarette smoke, endotoxin, or TNF-α.[42,57,72–74] Several studies[74–82] *in vivo* and *in vitro* have suggested that IL-8 and GRO-α, acting via their receptors, CXCR1 and CXCR2, are important mediators of neutrophil chemotaxis, endothelial cell adhesion, and degranulation. Evidence for neutrophil chemoattractant

roles of IL-8 and GRO-α was provided in several animal studies. For example, treatment with CXCR2 antagonist GRO-α(8–73) or a neutralizing anti-IL-8 antibody reduced the neutrophilic inflammation and alveolar damage and decreased mortality associated with endotoxinemia, acid aspiration, and in a skin air pouch model.[79,82,83] In addition, CXCR2-deficient mice show an impaired neutrophilic influx and myeloperoxidase activity in wounds after skin injury.[84]

In addition to neutrophil chemoattractant properties, IL-8 and GRO-α may be involved in wound repair and angiogenesis. Thus, skin, colon, and lung epithelial cells as well as endothelial cells express CXCR2.[85–92] Secondly, activation of CXCR2 by IL-8 and GRO-α can stimulate epithelial proliferation, migration, endothelial migration, and neovascularization.[85–87,89,93] CXCR2-deficient mice show delayed skin wound healing and neovascularization *in vivo*, and CXCR2-deficient keratinocyte cultures exhibit delayed repair that was not improved by mouse GRO-α.[84] Also, only basally located, nondifferentiated keratinocytes in human skin wounds *in vivo* showed CXCR2, coinciding with high expression of IL-8 and GRO-α.[88,94]

Thus, IL-8 and GRO-α are primary mediators in neutrophilic inflammation acting via CXCR1 and CXCR2. In contrast, CXCR2 is involved in epithelial repair. Several receptor antagonists or anti-IL-8 antibodies have been developed, but these have so far been reported only in assays *in vitro* or animal models.[78–80,82,95] Clinical trials in rheumatoid arthritis and psoriasis with humanized antibodies against IL-8, or CXCR2 antagonists are being conducted. Such agents may also represent potential therapeutic agents for COPD. As noted above, however, such agents may be contraindicated in patients with bacterial infections, as CXCR2 antagonist treatment of mice infected with *Pseudomonas aeruginosa* showed impaired pulmonary bacterial clearance.[96]

With regard to COPD, we observed that CXCR2 but not CXCR1 protein and messenger RNA are present in bronchial epithelial cells, mainly in injured areas[90] (Fig 2). In the same patients, IL-8 expression was significantly higher in bronchial epithelium from COPD patients as compared to smokers without COPD.[30] Preliminary functional analyses indicated that GRO-α but not IL-8 is mitogenic for bronchial epithelial cells, whereas both stimulate mitochondrial activity (unpublished observations). Given that IL-8 and GRO-α are capable of stimulating directly epithelial wound repair via CXCR2, such an antagonist therapy in COPD may impair this repair. CXCR1, although expressed primarily in neutrophils, is also expressed in macrophages, mast cells, and CD8+ T cells.[97,98] Specific antagonists for CXCR1 inhibit both the respiratory burst and degranulation of neutrophils.[78] Hence, CXCR1 antagonists, rather than CXCR2 antagonists, may be a more effective approach to reducing airways inflammation in COPD.

CC Chemokine and CCR2-Based Therapy

Macrophages and monocytes express several chemokine receptors, including CCR1, CCR2, and CCR5. Ligands for these receptors include MIP-1α, MIP-1β, MCP-1 to MCP-4, and RANTES (regulated on activation, normal T-cell expressed and secreted) [Table 1]. These chemokines stimulate monocyte/macrophage migration *in vitro*. Despite this chemokine and receptor redundancy, studies[99–102] *in vivo* indicate that MCP-1 and CCR2 are important monocytes and macrophage chemoattractants. Mast cells and T cells can also be attracted and activated by MCP-1.[103,104] CCR2 is the only known receptor for MCP-1.[105,106] MCP-1 is produced by several cell types including alveolar macrophages, epithelial, endothelial, and smooth-muscle cells, and fibroblasts.[30,107] MCP-1 expression can be induced by various cytokines, including TNF-α and IFN-γ.[56,108] In contrast, the expression of CCR2 is inhibited by IFN-γ.[109] This may represent an anti-inflammatory reaction preventing excessive influx of macrophages into the tissue. Different studies *in vivo* support specific roles of MCP-1 and CCR2 in macrophage migration. First, in mice with experiment peritonitis, the influx of monocytes and macrophages but not neutrophils, eosinophils, mast cells, or T cells, was impaired in MCP-1- or CCR2-deficient mice as well as in mice pretreated with antibody against CCR2.[99–102] In addition, bacterial clearance was impaired in CCR2-deficient mice, pointing to the importance of macrophages for bacterial clearance.[100] Secondly, transgenic mice with targeted overexpression of MCP-1 in type II pneumocytes showed increased numbers of monocytes, macrophages, and lymphocytes but not neutrophils in the lungs.[110] Third, ovalbumin-sensitized mice repeatedly exposed to ovalbumin showed an influx of monocytes/macrophages and lymphocytes into the lung coinciding with increased MCP-1 and MIP-1α expression. This influx was almost completely inhibited in mice pretreated with antibodies against MCP-1, but not with anti-MIP-1α.[111] Also, bronchial hyperreactivity was reduced by anti-MCP-1. Finally, Hautamaki et al[112] showed, in a murine emphysema model, that intratracheal MCP-1 increased both the numbers of lung macrophages and the smoke-induced emphysema, presumably via macrophage-derived MMP-12. These studies support the specificity of the MCP-1-CCR2 system rather than MIP-1α in recruitment of monocytes and macrophages.

Other effects of MCP-1 include stimulation of endothelial wound healing by inducing endothelial migration,[113] angiogenesis,[114] induction of vascular smooth-muscle hyperplasia,[115] collagen and transforming growth factor-β expression by fibroblasts,[116] and expression of adhesion molecules CD11c and CD11b as well as IL-1 and IL-6 by blood monocytes.[117] Our own studies[30] revealed expression of CCR2 on human bronchial epithelial cells. Preliminary data indicated that a signal transduction enzyme, mitogen-activated protein kinase p42/44, is phosphorylated in bronchial human epithelial cells upon MCP-1 treatment *in vitro*, and MCP-1 slightly but significantly induced epithelial proliferation. This indicates that CCR2 receptors are functional in airway epithelial cells and, moreover, that MCP-1 may have an autocrine effect on epithelial cells. These data further support a major role for MCP-1 and CCR2 in airway remodeling and inflammation directly or via macrophages. Antagonists of CCR2 or MCP-1 may, therefore, be an attractive approach to therapeutic treatment of COPD.

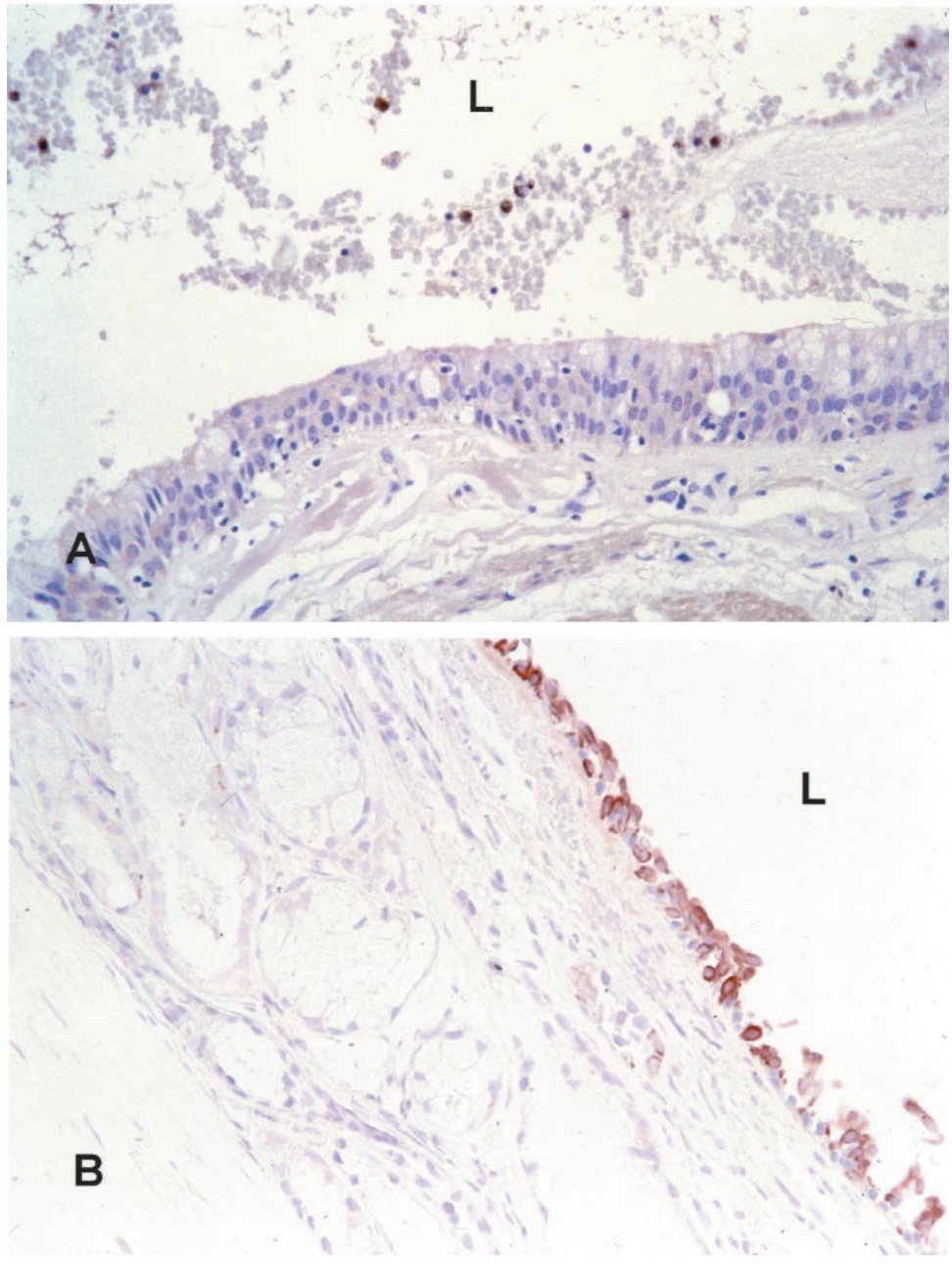

FIGURE 2. Expression of CXCR2 in airway epithelium. CXCR2 protein expression as detected by immunohistochemistry is shown in human bronchial tissue in intact epithelium (*top*, *A*) and damaged epithelium (*bottom*, *B*). Note the intense staining in regenerating epithelium (*bottom*, *B*) as compared to the virtual absence in intact epithelium (*top*, *A*). The brown (3,3′-diaminobenzidine)-stained cells in the airway lumen (*top*, *A*) are neutrophils. L = airway lumen (original × 200).

Several antagonist of MCP-1 and CCR2 have been described.[102,118,119] These include nonpeptide CCR2-specific antagonists,[119] CCR2 neutralizing antibodies,[120] MCP-1 peptide analogs,[118] and commercially available MCP-1 neutralizing antibodies. In several mouse models, these molecules show improvements of clinical and histologic symptoms in peritonitis,[102] arthritis,[121] allergic airways inflammation and hyperresponsiveness,[111] and bacterial clearance.[100] However, clinical trials with these molecules have not been reported. In diseases such as *Mycobacterium tuberculosis* infection, however, these antagonists may not be effective, as seen in infected MCP-1 deficient mice.[101] In addition, as MCP-1 seems to be involved in wound repair, inhibition of MCP-1 may also retard the healing.

CONCLUSION

As Scanlon et al[122] described, sustained smoking cessation improves lung function as compared to subjects who continue to smoke. However, for many smokers, stopping smoking is difficult. New therapies may prove to be more

effective than therapies such as glucocorticosteroids. Although chemokines show extensive redundancy, several studies[65,66,79,82,99,110,111] *in vivo* demonstrate the specificity of MCP-1 migration and activation of macrophages and monocytes, of IL-8 and GRO-α to neutrophils, and TNF-α to macrophages and neutrophils. Thus, treatment of COPD with chemokine or cytokines inhibitors may provide advantages over glucocorticosteroids. In order to reduce both macrophage and neutrophil numbers and activation, combinations of antagonists may be necessary. Long-term efficacy and safety studies with the anti-TNF-α therapies in humans are, however, lacking. Case reports may provide insight into side effects of these treatments.[63,123] In addition, any impairment of pulmonary bacterial clearance may indicate a need for concomitant administration of antibiotics. Furthermore, from the human studies with anti-TNF-α agents performed so far, it can be concluded that such treatments should be continual as the disease activity is only suppressed during treatment. Future clinical trials may provide encouraging data on novel treatments for COPD with one or more chemokine or cytokine antagonists.

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