Effects of matrix metalloproteinase inhibitor on LPS-induced goblet cell metaplasia

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Kim, Je Hyeong, Sung Yong Lee, Sang Myeon Bak, In Bum Suh, Sang Yeub Lee, Chol Shin, Jae Jeong Shim, Kwang Ho In, Kyung Ho Kang, and Se Hwa Yoo. Effects of matrix metalloproteinase inhibitor on LPS-induced goblet cell metaplasia. Am J Physiol Lung Cell Mol Physiol 287: L127–L133, 2004. First published March 12, 2004; 10.1152/ajplung.00047.2003.—Bacterial infections of the lung are known to induce inflammatory responses, which lead to mucus hypersecretion. Moreover, mucin synthesis in the airways has been reported to be regulated by neutrophilic inflammation-induced epidermal growth factor receptor (EGFR) expression and its activation. Furthermore, matrix metalloproteinases (MMPs), especially MMP-9, have been reported to promote the transmigration of activated neutrophils. In this study, we investigated the associations between lipopolysaccharide (LPS)-induced goblet cell (GC) metaplasia and EGFR expression and the effects of MMP inhibitor (MMPI). Various concentrations of LPS were instilled into the tracheas of pathogen-free Sprague-Dawley rats, and airways were examined at different times after LPS instillation. To examine the role of MMP-9, we treated rats 3 days before LPS instillation and daily thereafter with MMPI. Neutrophilic infiltration, Alcian blue/periodic acid-Schiff (AB/PAS) staining, and immunohistochemical staining for MUC5AC, EGFR, and MMP-9 were performed. The instillation of LPS increased AB/PAS and MUC5AC staining in time- and dose-dependent manners, and treatment with MMPI significantly prevented GC metaplasia. The instillation of LPS into the trachea also induced neutrophilic infiltration and EGFR and MMP-9 expression in the airway epithelium, and MMPI was found to significantly prevent neutrophil recruitment, GC metaplasia, and EGFR and MMP-9 expression. This study demonstrates that the MMP-9 and EGFR cascades are associated with LPS-induced mucus hypersecretion.

MUCUS SECRETION PLAYS an important role in mucosal protection. Mucin forms a viscoelastic gel that spreads over the airway luminal surface and interacts with cilia to form the mucociliary transport system. However, in chronic inflammatory airway diseases, excessive mucous secretion accumulates and contributes to the pathogenesis of acute asthma, chronic obstructive pulmonary disease, nasal polyps, cystic fibrosis, and bronchiectasis (33). Bacterial infections of the lung are also known to induce inflammatory responses, which lead to the overproduction of mucus. It was reported that a single instillation of Pseudomonas aeruginosa lipopolysaccharide (LPS) into the murine lung induces neutrophilic inflammation and causes goblet cell (GC) metaplasia and hyperplasia (62). Recently, mucin synthesis in the airways was reported to be regulated by the epidermal growth factor receptor (EGFR) cascade. The expression of EGFR in the bronchial epithelium is increased by activated neutrophils, and the activation of EGFR tyrosine kinase by its ligands or by oxidative stress leads to mucus hypersecretion and GC metaplasia (50, 52, 53, 55). This mechanism has been examined in cigarette smokers (55), in conditions of oxidative stress (53), and in allergic models (50, 52) and has been observed in human nasal polyps (6) and in asthmatic subjects (54). But in the case of LPS-induced GC metaplasia, the role of the EGFR cascades has not been examined.

The instillation of LPS into the lung induces the release of inflammatory mediators (22), which leads to the activation of neutrophils and endothelial cells. These activated neutrophils adhere to the pulmonary endothelial cell layer and migrate through the interendothelial cell junctions down to the underlying basement membrane. Moreover, neutrophils reaching the basement membrane transverse it by some undetermined mechanism (21, 59). Matrix metalloproteinases (MMPs) have been postulated to participate in this process. It was reported that MMP-9 is a major factor of polymorphonuclear neutrophil (PMN) migration across the basement membrane (11) and that MMP-9 inhibition by the MMP inhibitor (MMPI) reduces neutrophil transmigration (23), suggesting that MMP-9 has an important role in neutrophilic inflammation.

The present study was performed to explore the relationship between EGFR expression and LPS-induced GC metaplasia and the effects of MMPI on neutrophilic inflammation and EGFR expression in the pathogenesis of GC metaplasia and mucus hypersecretion.

MATERIALS AND METHODS

Study animals. Specific pathogen-free, male Sprague-Dawley rats, weighing 280–320 g, were purchased from Bio Genomic (Seoul, Korea). Animals were housed in pathogen-free rooms and maintained on laboratory chow with free access to food and water. The Animal Research Committee of Korea University approved all procedures.

LPS-induced GC metaplasia. Studies were performed in rats in vivo and showed that LPS induces GC metaplasia in rat airways. Animals were anesthetized with thiopental (37 mg/kg ip) and allowed...
to breathe spontaneously. Phosphate-buffered saline (PBS) or LPS (P. aeruginosa serotype 10; Sigma, St. Louis, MO) was instilled intratracheally via a 20-gauge Angiocath catheter (Becton Dickinson, Sandy, UT) through the mouth while the laryngeal area was visualized with a high-intensity illuminator (FiberLite; Dolan Jenner Industries, Lawrence, MA). To determine dose response, 200 or 300 μg of LPS were instilled into the trachea in 300 μl of PBS, and to determine time response, rats were euthanized at 3, 5, and 7 days after LPS instillation, and their airways were examined. The dose and time taken to achieve maximal GC metaplasia were then determined by

**MMPI** 6-Demethyl-6-deoxy-4-dedimethylaminotetracycline (CMT-3, donated by Collagenex Pharmaceuticals), was administered. This is a chemically modified, nonantibiotic tetracycline and was gavaged at 20 mg/kg in 1 ml of vehicle, which consisted of N-methyl pyrrolidine, propyl paraben, methyl paraben, ethanol, and 2% carboxymethyl cellulose, daily from 3 days before LPS instillation to the day of death.

**Tissue preparation.** Animals were euthanized with lethal dose of thiopental (200 mg/kg ip), and the systemic circulation was perfused with 1% paraformaldehyde in diethylpyrocarbonate (Sigma)-treated PBS via the left ventricle. We prepared paraffin sections by placing excised lung tissues in 4% paraformaldehyde overnight, dehydrating them with ethanol, and embedding them in paraffin. The embedded tissues were then sectioned at 4 μm and placed on glass slides.

**Evaluation of standard morphology, GC metaplasia, and neutrophil infiltration.** Paraffin sections were deparaffinized and stained with a Diff-Quik stain set (International Reagent) for morphologic study and stained with Alcian blue/periodic acid-Schiff (AB/PAS) for mucous glycoconjigates. To evaluate the recruitment of neutrophils, we stained sections with 3,3′-diaminobenzidine and counterstained them with toluidine blue. Neutrophils, which were observed as peroxidase-positive blue cytoplasmic cells, were counted in 10 consecutive high-power fields (HPFs, ×400) of the epithelium (50).

**Immunohistochemical staining for MUC5AC, EGFR, and MMP-9.** After blocking the activity of endogenous peroxidase with 0.3% H2O2 in methanol, we incubated sections with mouse monoclonal antibodies to EGFR (1:200; Calbiochem, San Diego, CA), MUC5AC (clone 45 M1, 1:500; New Markers, Fremont, CA), or MMP-9 (dilution 1:500; Oncogene Science, Cambridge, MA) in PBS containing 0.05% Tween 20 and 2% normal goat serum overnight at 4°C and then washed them with PBS to remove excess primary antibody. The sections were then incubated with biotinylated horse anti-mouse IgG (Vector Laboratories, Burlingame, CA) at a dilution of 1:200 for 1 h at room temperature. Bound antibody was visualized by a standard avidin-biotin-peroxidase complex protocol.

**Quantification of stained areas in the bronchiolar epithelium.** AB/PAS-stained areas and those of MUC5AC, EGFR, and MMP-9 immunoreactivities were quantified with a semiautomatic imaging system (30). Sections were counted by a single blinded observer on two separate occasions in a coded randomized order, as described previously (19). Images of the bronchiolar epithelium were recorded on 10 HPFs at ×400. AB/PAS-, MUC5AC-, EGFR-, and MMP-9-stained areas and the total bronchiolar epithelial area were measured and are expressed as percentages of the areas stained by: AB/PAS, antibody to MUC5AC, antibody to EGFR, or antibody to MMP-9. We performed analyses using the National Institute of Health's IMAGE program (30).

**Protocol.** The control group (n = 6) was composed of animals that has been subjected to sterile PBS (300 μl) instillation into the trachea and that had been gavaged with 1 ml of vehicle. After examining the lung tissues obtained from the preliminary dose- and time-response study, we determined the optimal dose and time of death. The LPS group (n = 7) consisted of animals that had been instilled with a predetermined dose of LPS in PBS (300 μl) and gavaged with 1 ml of vehicle. The LPS + MMPI group (n = 7) consisted of animals instilled with a predetermined dose of LPS in PBS (300 μl) and gavaged with 20 mg/kg of CMT-3 in vehicle (total volume 1 ml).

**Statistical analysis.** All data are expressed as means ± SE. Statistical analyses were performed with the nonparametric Mann-Whitney U-test to determine intergroup differences. A P value of <0.05 was taken to be statistically significant.

**RESULTS**

**LPS-induced GC metaplasia.** Preliminary studies were performed to determine the dose and time response of LPS instillation-induced GC metaplasia in the airways. After instilling 200 μg of LPS in 300 μl of PBS, we found the degrees of AB/PAS staining on days 3, 5, and 7 to be 42.31 ± 3.36, 45.46 ± 2.24, and 63.13 ± 4.6%, respectively. Seven days after 300 μg of LPS were instilled, the degree of AB/PAS staining in bronchial epithelium was 71.6 ± 2.56% (Fig. 1). Therefore, we adopted 300 μg as the optimal LPS dose and day 7 after LPS instillation as the time of death.

**GC metaplasia, as determined by AB/PAS staining in the control, LPS, and LPS + MMPI groups was 3.57 ± 2.36, 71.6 ± 2.56, and 14.73 ± 4.33%, respectively, which was significantly different in all three groups (P = 0.001 by the Kruskal-Wallis test). On comparing the groups, we found the LPS group to have significantly increased GC metaplasia over the control and the LPS + MMPI groups (P = 0.001 compared with control, P = 0.02 compared with the LPS + MMPI group). Furthermore, the LPS + MMPI group showed a higher AB/PAS staining level than the control (P = 0.038, Figs. 1 and 5).

**Expression of MUC5AC.** MUC5AC expressions in the bronchial epithelium of the control, LPS, and LPS + MMPI groups were 5.46 ± 4.68, 75.32 ± 4.53, and 11.46 ± 4.68, respectively, which was significantly different between all three groups (P = 0.001 by the Kruskal-Wallis test). The LPS group...
showed significantly more expression than the control and the LPS groups \((P = 0.02\), compared with the control and the LPS + MMPI group), and the control and the LPS + MMPI groups showed similar expression levels \((P = 0.067, \text{Figs. 2 and 5})\).

**Neutrophilic infiltration.** Neutrophilic infiltration in 10 HPFs of the control, LPS, and LPS + MMPI groups was \(6.64 \pm 2.87, 172.45 \pm 3.63, \text{and } 43.58 \pm 4.15\), respectively, which was significantly different between all three groups \((P = 0.001 \text{ by the Kruskal-Wallis test})\). The LPS group showed significantly higher levels of neutrophilic infiltration than the control and the LPS + MMPI groups \((P = 0.001, \text{compared with the control and the LPS + MMPI group})\). Neutrophils were predominantly located at basement membrane. The LPS + MMPI group showed more neutrophilic inflammation than the control \((P = 0.02, \text{Fig. 3})\).

**EGFR and MMP-9 expression in the bronchiolar epithelium.** In the control and the LPS + MMPI groups, no EGFR immunoreactivity was observed in tissues. Tissues in the LPS group expressed EGFR immunoreactivity in the bronchiolar epithelium. The mean percentage area of bronchiolar epithelium showing EGFR-positive staining was \(24.54 \pm 5.78\%\) \((\text{Figs. 4 and 5})\).

MMP-9 immunoreactivity was not expressed in the bronchial epithelium of the control group. However, in the LPS and LPS + MMPI groups, the expressions of MMP-9 were \(90.58 \pm 4.22\) and \(24.58 \pm 6.42\%\), respectively, indicating that MMP-9 was significantly downregulated by MMPI treatment \((P = 0.03, \text{Figs. 4 and 5})\).

**DISCUSSION**

In the present study, a single intratracheal LPS instillation induced neutrophilic inflammation and GC metaplasia in rat airways, as demonstrated by increased AB/PAS staining and MUC5AC expression. This phenomenon was closely associated with increased immunoreactivity of MMP-9 and EGFR.

Moreover, MMPI treatment significantly inhibited GC metaplasia and downregulated MMP-9 and EGFR expression in the bronchial epithelium.

Despite the importance of GC metaplasia in airways, analysis of the mechanisms of GC production has proven to be difficult, because of the heterogeneity of hypersecretory disease. Hence, the precise mechanisms causing GC metaplasia in hypersecretory disease remain unknown. Currently, the biochemical and molecular mechanisms of airway hypersecretion are the subjects of intensive investigations, and it is hoped that such studies will lead to new therapeutic strategies. Mucus hypersecretion from metaplastic GCs causes airway mucus plugging in the peripheral airways of rodents \((5)\) and contributes to the morbidity and mortality of chronic inflammatory airway diseases in humans \((1, 15, 42, 51)\). Many stimuli, such as LPS, induce a single intratracheal LPS instillation induced neutrophilic inflammation and GC metaplasia in rat airways, as demonstrated by increased AB/PAS staining and MUC5AC expression. This phenomenon was closely associated with increased immunoreactivity of MMP-9 and EGFR.

**Fig. 2.** Expression of MUC5AC in bronchial epithelium. MUC5AC expression was significantly increased in the LPS group. MMPI markedly decreased MUC5AC expression. *\(P < 0.05\) compared with the control and the LPS + MMPI group, **\(P < 0.05\) compared with the LPS group, †\(P > 0.05\) compared with the control group.

**Fig. 3.** Neutrophilic infiltration. The LPS group showed significantly increased neutrophilic infiltration compared with the control and the LPS + MMPI groups. Neutrophilic infiltration was significantly increased in the LPS + MMPI group vs. the control. *\(P = 0.001\) compared with the control and LPS + MMPI groups, **\(P = 0.02\) compared with the control group. HPF, high-power field.

**Fig. 4.** Expression of epidermal growth factor receptor (EGFR) and matrix metalloproteinase-9 (MMP-9). EGFR was expressed only in the LPS group, but MMP-9 expression was observed in the LPS and the LPS + MMPI group, although this was significantly lower in the LPS + MMPI group. *\(P = 0.03\) compared with the LPS group.
as bacterial LPS (27), cytokines (10, 50, 56), and elastase (24), are known to induce mucus secretion. GC metaplasia has been reported to be generated in mouse lungs by a single intratracheal instillation of *P. aeruginosa* LPS (62). In response to LPS challenge, the inflammatory cells migrate in large numbers to the lung. Yanagihara et al. (62) reported that a single intratracheal instillation of *P. aeruginosa* LPS induced the migration of circulating neutrophils, macrophages, and lymphocytes to the lung in a mouse model. In another report, Blyth and colleagues (5) found that a single intratracheal instillation of *Escherichia coli* LPS in BALB/c mice was followed by a significant neutrophil influx into the lung lumen. In the present study, a single intratracheal instillation of *P. aeruginosa* LPS induced GC metaplasia in a dose- and time-dependent manner as well as significant neutrophilic infiltration in rat airways.

In 1999, Takeyama et al. (52) reported that EGFR expression and activation in the airway epithelium are responsible for mucus hypersecretion. In vitro and in vivo studies have shown that proinflammatory cytokine tumor necrosis factor-α (TNF-α), the production of which is attributed to neutrophilic inflammation, upregulated EGFR expression and its ligands, transforming growth factor-α or EGF, and induced GC metaplasia. However, stimulation with EGFR ligands alone was found to be insufficient to induce GC metaplasia. The activation of EGFR can occur by ligand-dependent autophosphorylation mediated by EGFR ligands or by ligand-independent transactivation mediated by various stimuli including oxidative stress (H₂O₂). The subsequent activation of EGFR tyrosine kinase induces the mucin *MUC5AC* gene and *MUC5AC* protein expression and GC metaplasia in vitro and in vivo (6, 50, 52–55). The present study also showed that increased neutrophilic inflammation is closely related to upregulated expression of EGFR in the bronchial epithelium and that GC metaplasia, as assessed by AB/PAS and MUC5AC staining, was significantly enhanced. According to these results, LPS-induced GC metaplasia in rat airways is closely associated with neutrophilic inflammation-mediated EGFR expression in the bronchial epithelium.

The metalloproteinases are important agents in many respects of biology. They participate in cell proliferation and differentiation and in the remodeling of the extracellular matrix (ECM), vascularization, and cell migration. Moreover, because...
metalloproteinase has been to regulate autocrine signaling through EGFR by ligand release (13), and G protein-coupled receptor (GPCR)-induced EGFR transactivation in cells is sensitive to pretreatment with the broad-spectrum metalloproteinase inhibitor batimastat. Metalloproteinases have been suggested to have a cardinal role in receptor cross talk (37).

There are two closely related metalloproteinase families: MMPs and metalloproteinase-disintegrins (ADAMs). ADAMs are transmembrane proteins characterized by a zinc-dependent metalloproteinase, an adhesion domain, a fusion domain, and an intracellular signaling domain (4). Studies about the function of ADAMs have focused on regulating growth signaling. ADAM10 has been reported to mediate the transactivation of EGFR by GPCR (61). Moreover, the proteolysis of membrane-bound pro-heparin-binding EGFR by ADAM10 and the following EGFR phosphorylation were found to increase mucin MUC2 gene transcription in a colon tumor cell line (26). Recently, TNF-α-converting enzyme (TACE), also called ADAM17, was reported to play a critical role in mucin production by airway epithelial cells by means of a TACE ligand-EGFR cascade triggered by various stimuli (49).

MMPs are a group of zinc- and calcium-dependent enzymes known for their ability to cleave one or several ECM constituents. Moreover, the exuberant or aberrant expression of MMPs can cause tissue damage and has been reported to be associated with a variety of lung diseases. MMPs can be classified on the basis of sequence homology and substrate specificity into four groups: interstitial collagenase, PMN collagenase, collagenase-3, and membrane-type metalloproteinases (12). In contrast to ADAMs, studies to date have provided compelling evidence about MMP activity, especially in terms of the identities of participating MMPs, through their physiological relevance with respect to signaling processes remains elusive. Nevertheless, it was reported that MMP-2 and MMP-9 mediate EGFR transactivation by gonadotropin-releasing hormone (38); the role of MMPs in EGFR signaling requires further studies. We preferentially intend to investigate peculiar activity of neutrophil collagenase with respect to the neutrophilic inflammation-induced EGFR activation. Neutrophil collagenase consists of the 72-kDa and 92-kDa gelatinases gelatinase A (MMP-2) and gelatinase B (MMP-9), respectively. MMP-2 is synthesized by a wide variety of cells, including fibroblasts, endothelial cells (44), and alveolar epithelial cells (32, 63). Moreover, MMP-9 is produced mainly by inflammatory cells such as PMNs, monocytes, macrophages, eosinophils, and lymphocytes (14, 34, 57). In particular, activated neutrophils secrete significant amounts of MMP-9, a major elastolytic MMP (46), but not MMP-2 (35).

Neutrophil migration into sites of inflammation is a crucial feature of host defense against microorganisms, and failure of migration is associated with marked increase in life-threatening infections (16). The pulmonary consequence of neutrophil accumulation has not been completely elucidated. It is well accepted that leukocyte migration from the vasculature occurs via a multistep process, dictated by the sequential activation of adhesive proteins and their ligands on both leukocytes and endothelial cells. Monocytes, lymphocytes, and neutrophils all migrate by a similar, sequence-dependent mechanism. The initiation of migration begins with “capture” by the vessel wall of neutrophils in the flowing blood, and this is followed by their “rolling” along the vessel wall. This process of margination is a normal behavior of circulating neutrophils. Only after appropriate stimuli are present do rolling leukocytes become firmly adhered to endothelial cells and thus positioned to migrate from a blood vessel into the tissue parenchyma (58). The mechanism of pulmonary neutrophil migration in rats given intratracheal LPS has been partially characterized and involves airway cells producing inflammatory cytokines like TNF-α and IL-1β and neutrophil-specific chemoattractants known as CXC chemokines (18). Although it has been reported that interaction with β2- and β3-integrin might also be important for the transit of neutrophils through the extravascular milieu (47, 48), there is relatively little known of the mechanism of neutrophil egress and migration through the subendothelial matrix. Neutrophils possess proteases capable of digesting collagen, laminin, and other extracellular components. Adhesion and migration are accompanied by the release of neutrophil-derived proteases (20, 60), and both chemotaxis and migration through artificial substrates in vitro are inhibited by treatment with antiproteases (29). Hence, a critical role has been proposed for neutrophil-derived protease activity during extravascular transit, and studies have so far provided compelling evidence that MMP-9 activity can induce or enhance the migration of neutrophils.

According to some studies, MMP-9 is a major factor of neutrophil migration across the basement membrane in vitro (11) and promotes neutrophil migration in pancreatitis-associated lung injury in the rat (23). However, MMPi is ineffective at stopping neutrophil migration through intact endothelial cell monolayers and basement membrane matrices in vitro (31), and neutrophils from MMP-9-deficient mice showed no defect in transendothelial migration in vitro (2). Furthermore, mice deficient in MMP-9 have normal neutrophil emigration into the lungs, peritoneum, and skin (3). Thus the role of MMP-9 release and digestion of extravascular matrix components during migration is uncertain (58). Therefore, we undertook an investigation of the role of MMP-9 and MMPi in neutrophilic inflammation-mediated EGFR activation and subsequent mucus production.

In the present study, the degree of MMP-9 expression showed a close correlation with neutrophilic infiltration and in the predominant localization of neutrophils at bronchiolar basement membrane in the LPS group, suggesting that activated neutrophils migrate through the extravascular milieu aided by digestion with MMP-9. In the case of CMT-3 treatment, MMP-9 expression and neutrophilic infiltration were significantly decreased, suggesting that MMPi prevents neutrophilic migration. The attenuation of neutrophilic infiltration by MMPi was related to a decrease in GC metaplasia and the downregulation of EGFR expression in the bronchial epithelium.

Several studies have reported some direct relationship among LPS, MMPs, and EGFR. In different cell types in vitro, a number of reports have demonstrated the effects of LPS on MMP expression (17, 39, 41, 43). In mice, LPS administration increased various MMP gene expression in parenchymal cells of the kidney, liver, spleen, and brain (36). It was reported that a selective EGFR tyrosine kinase inhibitor and an EGFR-neutralizing antibody prevents P. aeruginosa LPS-induced mucin synthesis in human airway epithelial cells, implicating EGFR activation (25, 49). These direct effects might participate in the pathogenesis of LPS-induced GC metaplasia, and
multiple pathways activated by LPS could be important in mediating GC metaplasia. In the present study, we initially investigated the relationship between LPS-induced neutrophilic inflammation and EGFR expression by MMP-9 in vivo. CMT-3, used as an MMPI in the present study, is a non-antimicrobial tetracycline chemically modified to enhance its collagenase-inhibitory property. Because CMT-3 is a relatively new drug, its mechanisms of action are still being elucidated. It is a potent inhibitor of MMPs (9) and has been successfully used in the treatment of experimental diabetes in rats (40), prostate cancer in rats (28), and experimental lung injury in pigs (7, 8). The precise mechanism of MMP inhibition by CMT-3 is not fully understood. CMT-3 is the most potent new drug, its mechanisms of action are still being elucidated. In the present study, we investigated the relationship between LPS-induced neutrophilic inflammation and EGFR expression by MMP-9 in vivo. MMP-9 was blocked predominantly by CMT-3 treatment in neutrophilic invasion in the lungs, peritoneum, and skin does not require gelatinase B. Metalloprotease-mediated ligand release regulates autocrine and paracrine actions of TNF alpha and Notch.

In conclusion, in rat airways, intratracheal LPS instillation induces GC metaplasia, which is associated with increased neutrophil infiltration and MMP-9 and EGFR expression. Moreover, in the case of MMPI treatment, decreased GC metaplasia is closely associated with the downregulation of EGFR expression together with reduced of MMP-9 expression and neutrophilic infiltration.

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