Mucins are the major components of the mucous layer that covers and protects the respiratory, digestive, and reproductive tracts. Our previous studies showed that MUC8 gene expression was overexpressed in *in vivo* polyep epithelium in chronic sinusitis and was also increased by treatment with inflammatory mediators in *in vitro* culture condition. However, the mechanisms by which the inflammatory mediators-induced MUC8 gene expression in normal nasal epithelial cells evolved remain unclear. We examined the mechanism by which the important proinflammatory mediator, interleukin (IL-1β), influences MUC8 gene expression levels. We found that pharmacologic and genetic inhibition of ERK MAPK pathway abolished IL-1β-induced MUC8 gene expression in normal human nasal epithelial cells. Moreover, the overexpression of wide-type or the dominant-negative mutant of p90 ribosomal S6 protein kinase 1 (RSK1) enhanced or suppressed, respectively, IL-1β-induced MUC8 gene expression. RSK1 was found to directly phosphorylate cAMP-response element-binding protein (CREB), and this event led to the stimulation of subsequent CRE-mediated gene transcription. In conclusion, IL-1β was found to induce MUC8 gene expression via a sequential ERK/RSK1/CREB pathway in human airway epithelial cells.

Mucins are highly glycosylated, high molecular mass glycoproteins and are major components of the mucus produced by the epithelia of the respiratory, gastrointestinal, and reproductive tracts. They are responsible for the viscoelastic properties of secreted mucus and provide lubrication and protection for mucus membranes (1). In the airway, virtually all forms of airway inflammation are associated with the overproduction of mucus, which can lead to airway obstruction (2).

Eighteen types of mucin genes have been discovered to date: MUC1 to MUC4, MUC5AC, MUC5B, MUC6, MUC7, MUC8 (2), MUC9 (3), MUC10 (4), MUC11, MUC12 (5), MUC13 (6), MUC15 (7), MUC16 (8), MUC17 (9), and MUC18 (10). Of these, MUC5AC and MUC5B are known to be major gel-foaming mucins secreted in the human airway. Accordingly, most studies on mucin genes have been focused on these two mucins. However, although MUC5AC is known to be expressed by most surface goblet cells, we found that only a portion of the goblet cells (11) expressed MUC5AC mRNA. This suggests that other mucin genes in addition to MUC5AC might be important for mucus hypersecretion. We have previously investigated the expressions of other mucin genes using various inflammatory tissues and cell lysates. Interestingly, in *vivo*, we found that MUC8 mRNA levels are clearly up-regulated in the polyp epithelium, which is invariably stimulated by inflammatory mediators (12). In addition, in *vitro*, interleukin-1β (IL-1β), tumor necrosis factor-α, and a mixture of inflammatory mediators were found to up-regulate MUC8 mRNA and to down-regulate MUC5AC mRNA (13, 14). These results showed that MUC8 mRNA is increased both in *vivo* and *in vitro* during inflammatory conditions. However, the mechanisms of MUC8 gene expression during inflammation in normal airway epithelial cells and the signal molecules involved have not been elucidated.

Mitogen-activated protein kinases (MAPKs) are ubiquitous kinases and are involved in signal transduction in eukaryotic organisms. This family of kinases is characterized by their activation by MAPKs through the dual phosphorylation of Thr and Tyr residues in their activation loop. The MAPK family includes extracellular signal-regulated kinases (ERK), which are activated in response to growth factors, via the Ras proto-oncogene. Moreover, c-Jun N-terminal kinase (JNK) and p38 MAPK constitute two other families, collectively known as stress-activated protein kinases (SAPK), because they are induced by UV radiation, heat-shock, oxidative stress, or tumor necrosis factor-α. The stimulation of ERK initiates a cascade of

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This study was supported by the 2002 Good Health R&D project, Ministry of Health and Welfare, South Korea (Grant 02-PJ1-PC3-20908-0005). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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PCR was performed on a PE Biosystems ABI PRISM 7700 Sequence Detection System (Foster City, CA). The thermocycler (ABI PRISM 7700 Sequence Detection System) was programmed with the following protocol: 50°C for 2 min, followed by 40 cycles of 95°C for 1 min, 55°C for 1 min, 72°C for 1 min. 

Western blotting was conducted as described by various stimuli may yield a deeper insight into cellular signaling. The procedure recommended by the manufacturer was followed. Stably transfected cell lines were harvested and was cultured in RPMI 1640 (Invitrogen) supplemented with 10% fetal bovine serum (PAA Laboratories). The culture system used for the normal human nasal epithelial cells was washed twice with phosphate-buffered saline (PBS) and was incubated at room temperature for 30 min with the 32P-labeled probe of real-time PCR was labeled with carboxytetramethylrhodamine (TAMRA). Real-time reverse transcription–PCR and TaqMan probe (6FAM-TGCTCGCG-CATTTAGT-TAMRA). 

Previously, ERK and p38 MAPKs had shown maximum activation after 15-min treatment with IL-1β. Western Blot Analysis—Western Blot Analysis was performed on the following proteins of MUC8 promoter regulation and was incubated at room temperature for 30 min with the 32P-labeled probe of real-time PCR. The probe of real-time PCR was labeled with carboxytetramethylrhodamine (TAMRA). Real-time reverse transcription–PCR and TaqMan probe (6FAM-TGCTCGCG-CATTTAGT-TAMRA).

**Detection System (Foster City, CA). The thermocycler (ABI PRISM 7700 Sequence Detection System) was programmed with the following protocol:**

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- 95°C for 2 min, followed by 40 cycles of
  - 95°C for 1 min, 55°C for 1 min, 72°C for 1 min.
the activation of JNK (18). To investigate the possible involvement of ERK or p38 MAPK pathway in IL-1β-induced MUC8 gene expression, we performed real-time PCR after pretreatment with 20 μM PD98059 or 20 μM SB203580 and then stimulated for 24 h with IL-1β prior to the collection of total RNA for the real-time quantitative PCR of MUC8. The figures shown are representative of three independent experiments.

When the same experiment (Fig. 1) was performed using NCI-H292 cells, a human lung mucoepidermoid carcinoma cell line, we obtained results that were similar to those of normal cells (data not shown). To further confirm the significance of ERK or p38 kinase upon the cellular level of MUC8 gene expression, we generated cells stably expressing dominant-negative (DN) mutant MEK1 or p38 under control of the Tet-off line, we obtained results that were similar to those of normal NCI-H292 cells, a human lung mucoepidermoid carcinoma cell line, we obtained results that were similar to those of normal cells (data not shown). To further confirm the significance of ERK or p38 kinase upon the cellular level of MUC8 gene expression, we generated cells stably expressing dominant-negative (DN) mutant MEK1 or p38 under control of the Tet-off system. After removing doxycycline to induce MEK1DN, cells were stimulated with IL-1β for 15 min, and IL-1β-induced phosphorylation of ERK significantly decreased (Fig. 2A). However, no change in ERK expression was observed. Real-time quantitative PCR showed a significant decrease in MUC8 gene expression after 24 h (Fig. 2A). In a similar way, we investigated the role of p38 MAPK on IL-1β-induced MUC8 gene expression using p38DN. An in vitro kinase assay showed that the activation of p38 MAPK in this mutant stable cell lines was reduced in the presence of IL-1β (Fig. 2B). However, the IL-1β-induced MUC8 gene expression was not affected by p38DN induction. These results showed that ERK MAPK, but not p38 MAPK, was essential for IL-1β-induced MUC8 gene expression in NCI-H292 cells. To examine whether the sequential Ras/RAF/MEK1/ERK pathway plays a role in IL-1β-induced MUC8 gene expression, we transiently transfected DNA with constructs encoding RasDN (Ras N17) or Raf1DN (raf1, a kinase-defective form of Raf1). The transient overexpressions of Ras or Raf1DN did not affect the IL-1β-activated phosphorylation of ERK MAPK (Fig. 2C), and the IL-1β-induced MUC8 gene expression (Fig. 2D). ECV304 cells were used as a positive control for these dominant-negative vectors (19). These results show that the activation of ERK MAPK via MEK1 by IL-1β might occur via a Ras-independent pathway to induce MUC8 gene expression in airway epithelial cells.

Effects of RSK1 on IL-1β-induced MUC8 Gene Expression—To determine which molecules are involved in the downstream signaling of ERK MAPK in IL-1β-induced MUC8 gene expression, we investigated RSK1 and MSK1. RSK1 has been reported to be activated by ERK MAPK (20–22). The phosphorylation of RSK1 by IL-1β peaked at 30 min and then decreased at 60 min after IL-1β stimulation (Fig. 3A). Pretreatment with 20 μM PD98059 inhibited IL-1β-activated RSK1 phosphorylation (Fig. 3B), indicating that RSK1 is regulated by ERK MAPK. These results showed that RSK1 acts as a downstream signaling mediator of ERK MAPK. To determine whether RSK1 plays an important role in IL-1β-induced MUC8 gene expression, an RSK1 mutant study was performed. RSK1 is currently a candidate for the mediation of cytokine-induced CREB phosphorylation at Ser133 (20, 23, 24). Overexpression of wide-type (WT) RSK1 increased IL-1β-induced CREB phosphorylation. However, the overexpression of RSK1DN (D205N) suppressed the IL-1β-induced CREB phosphorylation. Consistently, IL-1β-induced MUC8 gene expression was increased by overexpression of WT RSK1, whereas the IL-1β-induced MUC8 gene expression was significantly suppressed by RSK1DN (D205N) (Fig. 3C). These results show that RSK1 is required for IL-1β-induced MUC8 gene expression.

Effects of CREB on IL-1β-induced MUC8 Gene Expression—We examined whether IL-1β-activated RSK1 specifically binds to CREB in human airway cells. Cell extracts obtained after stimulation with IL-1β were immunoprecipitated with anti-phospho CREB antibody and then blotted with an anti-phospho RSK1 antibody. As shown in Fig. 4A, protein complex formation was observed between RSK1 and CREB. The control IgG was used as an immunoprecipitating antibody. In addition, a transient phosphorylation of CREB was observed upon the stimulation with IL-1β, reaching the maximum peak at 30 min. These results suggest that IL-1β-activated RSK1 leads to the phosphorylation of CREB in NCI-H292 cells. To confirm whether IL-1β-induced phospho-RSK1 is enzymatically active, we performed an immunocomplex in vitro kinase assay using bacterially expressed GST-CREB as a substrate. As shown in Fig. 4B, IL-1β-activated RSK1 activity remarkably increased in cells transfected with WT RSK1, whereas the overexpression of RSK1DN diminished IL-1β-induced RSK1 activity.

To determine whether CREB plays a role in MUC8 gene expression, we used both forskolin (an activator of adenylate cyclase) and 3-isobutyl-1-methylxanthine (IBMX, an inhibitor of AMP phosphodiesterase). The transient phosphorylation of CREB was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18). The CREB phosphorylation was observed after stimulation with both forskolin and IBMX, and this reached a maximum peak at 10 min (18).
body, respectively. Specific band was found to be selectively inhibited by the specific CRE competitor and to be supershifted by anti-phospho-CREB antibody. These results indicate that activated CREB binds to a *cis*-acting element, which we refer to as CRE. Next, we assayed the gene expression of the pCRE-luc construct to determine whether IL-1β exerts a stimulatory effect on the activation of CREB and on the subsequent CRE-mediated gene transcription. To investigate the role of CREB phosphorylation on CRE-mediated gene transcription, cells were transfected transiently with pCRE-luc vector only or both pCRE-luc vector and plasmid encoding CREB DN (S133A). Treatment of transfected NCI-H292 cells with IL-1β resulted in increased CRE-mediated gene transcription in a time-dependent manner (Fig. 5B). The expression of CREB containing a
mutation of the critical regulatory Ser133 residue was found to significantly inhibit the luciferase activity induced by IL-1β. Mock transfection, used as a negative control, showed no significant induction of CRE-mediated reporter transcription. These results suggest that IL-1β-activated CREB triggers CRE-mediated transcription by binding to CRE.

**DISCUSSION**

Mucociliary clearance is an important function of the airway epithelium. Human beings inhale noxious gases, air pollutants, bacteria, and viruses through the nose, and these are usually trapped by mucus and removed by ciliary beating toward the nasopharynx. Increased mucus secretion during inflammation may represent a defensive mechanism, and inflammatory mediators increase the ciliary beating of respiratory epithelial cells to promote mucociliary clearance (25–27).

The molecular mechanism by which MUC8 gene expression is up-regulated by IL-1β remains poorly understood. In the present study, we investigated the mechanisms by which MUC8 gene expression is up-regulated by IL-1β in normal human nasal epithelial cells. Our results show that only the activation of ERK MAPK was required for IL-1β-induced MUC8 gene expression, although several reports have concluded that more than one MAPK might be necessary for the signal transduction of various inflammatory mediators (28–30). Moreover, the ERK MAPK cascade is known to be activated by G-protein-coupled receptor via: (i) EGFR transactivation (Ras-dependent); (ii) a protein kinase C-dependent, but epidermal growth factor receptor- and Ras-independent, pathway; or (iii) a Ras-independent and cAMP/protein kinase A-mediated pathway (31). Of these pathways, the activation of ERK MAPK by MEK1, as induced by IL-1β, might occur via a Ras/Raf-independent pathway to induce MUC8 gene expression in human airway epithelial cells. Further work is necessary to explore these pathways.

To date, the signal molecules involved in the downstream signaling of ERK MAPK, for IL-1β-induced MUC8 gene expression, have not been yet identified. The role of RSK1 and CREB in the downstream signaling of ERK MAPK to induce MUC8...
FIG. 5. IL-1β-induced activation of CRE-mediated gene transcription via the cis-acting regulatory CRE motif. Confuent, quiescent cells were stimulated for 1 h with IL-1β. Nuclear proteins were incubated with CRE, a 50-fold excess of cold probe, or anti-phospho CREB antibody before EMSA. A, the labeled nuclear proteins were separated by electrophoresis on 5% polyacrylamide gels, and the gels were dried and autoradiographed at ~70 °C overnight. C, control; Ab, antibody; NS, nonspecific. B, when the cells were 70% confluent, pCRE-luc, or both pCRE-luc and CREB DN (pCREB S133A) plasmid, and empty parental control vector (mock) as a control, were transiently transfected into the NCI-H292 cells. Confuent cells were then stimulated with IL-1β for the indicated times, and the luciferase activity of the reporter plasmid was measured. Luciferase activities were determined after correcting for transfection efficiency versus the β-galactosidase activity of the cell lysates. The values shown are means ± S.D. of experiments performed in triplicate.

gene expression is a major finding of the present study. The substrates of ERK MAPK are known to be the MSK and RSK family members (33). Our results show that RSK1 might be essential for IL-1β-induced MUC8 gene expression. In addition, the activation of MSK1 appears to be closely related to IL-1β-induced MUC8AC gene expression by IL-1β in human airway epithelial cells (18). Differences in the activations of the kinase by IL-1β may be responsible for differences in target genes. RSK1 phosphorylates several transcription factors, including CREB (34), c-Fos (35), CCAAT/enhancer binding protein (36), nuclear factor-κB (21), and the estrogen receptor (37), and interacts with transcriptional coactivator CREB-binding protein (also known as p300) (38). Many studies have shown that RSK1 phosphorylates Ser133 of CREB (16, 39–41). Although CREB activation by RSK1 has been established by previous studies in other cells, and CREB is a potent regulator of mucin (MUC2, MUC5AC, MUC5B, and MUC6) gene expression in the p15 arm of chromosome 11 (11p15) (17), its role remains unclear in airway epithelial cells. In addition, little is known about the involvement of CREB in MUC8 gene expression. In the present study, the activation of CREB was found, at least in part, essential for IL-1β-induced MUC8 gene expression via ERK MAPK and RSK1. Interestingly, MUC8 gene expression was inhibited in CREB DN (S133A)-transfected cells treated with IL-1β. In addition, treatment with both forskolin and IBMX activated the phosphorylation of CREB and increased MUC8 gene expression (Fig. 4, C and D). These results suggest that CREB might be a transcription factor for IL-1β-induced MUC8 gene expression. However, increased MUC8 expression induced by both forskolin and IBMX was less than that induced by IL-1β, indicating that activation by CREB alone is insufficient for IL-1β-induced MUC8 gene expression. These results suggest that a transcription factor, other than CREB, may be required for IL-1β-induced MUC8 gene expression.

We examined whether IL-1β-induced MUC8 gene expression in human airway epithelial cells is a CRE-mediated transcription. We found that the IL-1β-induced phosphorylation of CREB had the DNA binding activity to CRE (Fig. 5A). Moreover, IL-1β-induced CRE activation increased in a time-dependent manner, whereas the overexpression of CREB DN mutant led to a ~90% decrease in the response of the CRE minimal promoter to IL-1β (Fig. 5B). These results showed that the activation of the cis-element, CRE, appeared closely related to IL-1β-induced MUC8 gene expression in human airway epithelial cells. These results indicate that the MUC8 promoter might have CRE site(s) and the CRE might be an important transcription factor of the MUC8 promoter, like the munc11 (11p15 chromosome) (17). However, unexpectedly, the promoter and cDNA sequences of the MUC8 gene have not yet been fully identified. Thus, further studies upon the MUC8 promoter seem warranted.

In summary, IL-1β was found to induce MUC8 gene expression via the MEK1/ERK pathway. Furthermore, the activations of RSK1 and CREB are a crucial aspect of the intracellular mechanisms that mediate MUC8 gene expression in human airway epithelial cells. Molecular cloning of the MUC8 promoter regulated by various stimuli may yield a deeper insight into ciliated cell differentiation or function.

Acknowledgment—We are deeply grateful to Dr. Jae-Hong Kim for the cDNA construct encoding dominant-negative Raf1 vector.

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