Anti-inflammatory effects of celecoxib in rat lungs with smoke-induced emphysema

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¶Department of Internal Medicine and Clinical Research Center for Chronic Obstructive Airway Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul; ∥Department of Internal Medicine, Ilsan Paik Hospital, Inje University, Goyang; and ∗Department of Internal Medicine, Bundang CHA Hospital, University of Pocheon Jungmoon College of Medicine, Seongnam, South Korea

Submitted 1 September 2009; accepted in final form 13 May 2010

Roh GS, Yi C, Cho YJ, Jeon BT, Nizamudtinnova IT, Kim HJ, Kim JH, Oh Y, Huh JW, Lee J, Hwang YS, Lee SD, Lee JD. Anti-inflammatory effects of celecoxib in rat lungs with smoke-induced emphysema. Am J Physiol Lung Cell Mol Physiol 299: L184–L191, 2010. First published May 14, 2010; doi:10.1152/ajplung.00303.2009.—Chronic airway inflammation is a characteristic feature of destructive cigarette smoking (CS)-induced lung disease, particularly in patients with emphysema. Celecoxib, a specific cyclooxygenase-2 (COX-2) inhibitor, is widely used to treat inflammation. However, the exact mechanisms underlying this drug’s anti-inflammatory effects have not yet been determined in pulmonary emphysema. Here, we explore whether celecoxib attenuates CS-induced inflammation in rat lungs. Rats were exposed to smoke and received celecoxib via intragastric feeding daily for 20 wk. We found that celecoxib inhibited interalveolar wall distance and pulmonary inflammation in the lungs of CS-treated rats. Celecoxib inhibited serum NO production, iNOS, COX-2 expression, and PGE2 production in CS-treated lung tissues. Our immunohistochemical data showed that CS-induced CD68 and COX-2 expression were inhibited by celecoxib. Furthermore, celecoxib attenuated the activation of phospho-IκBα and NF-κB in CS-treated rat lung. In addition, there was an inhibitory effect of celecoxib on the COX-2 expression and NF-κB activation in LPS-stimulated RAW 264.7 macrophages. Celecoxib also attenuated NF-κB activation in COX-2 siRNA-transfected RAW 264.7 macrophages. Thus, our findings suggest that the anti-inflammatory effects of celecoxib are mediated by its effects on NF-κB-regulated gene expression, which ultimately reduces the progression of CS-induced pulmonary emphysema.

Nitric oxide (NO) plays an important role in the regulation of a variety of physiological processes, including host defense and inflammation (20). NO production, along with the expression of inducible NO synthase (iNOS), is a key molecule that protects lungs from inflammation (26). In addition to upregulation of iNOS, cyclooxygenase (COX)-2 contributes to the pathophysiological progression of certain human cancers and inflammatory disorders (13, 37). The COX enzyme consists of two isoforms designated COX-1 and COX-2. COX-1 is predominantly involved in physiological and regulatory processes, whereas COX-2 is induced in a variety of healthy tissues by inflammatory cytokines, growth factors, and oncogenes (6, 35).

The NF-κB transcription factor plays an important role in the induction of genes involved in physiological processes, as well as in the body’s response to injury and inflammation. In its inactive state, NF-κB is a cytoplasmic heterodimer that consists of three subunits: p50, p65, and IκBα. In the presence of proinflammatory signals, IκBα is phosphorylated and degraded via the proteosomal pathway, thereby exposing nuclear localization signals on the p50-p65 heterodimer (32).

Nonsteroidal anti-inflammatory drugs (NSAIDs) relieve inflammation and pain and reduce prostaglandin biosynthesis via the inhibition of COX signaling. Selective COX-2 inhibitors have been developed as potentially gastro-safe NSAIDs (16, 19). A previous study demonstrated that staphylococcal enterotoxin B-induced acute pulmonary inflammation was reduced by pretreatment with celecoxib (5). These findings raised the possibility that dietary celecoxib could modulate the development of smoking-induced lung disease. Therefore, we investigated the effects of celecoxib in an animal model of pulmonary emphysema to determine whether celecoxib treatment attenuated the CS-induced changes in lung morphology, altered the expression of various proinflammatory genes, or modulated the activity of NF-κB signaling cascades.

MATERIALS AND METHODS

CS exposure and treatment groups. The protocols used in this animal study were approved by the Asan Medical Center’s Panel on Laboratory Animal Care. Male Sprague-Dawley rats (Orient, Seoul, South Korea), weighing between 220 and 250 g, were treated with whole body exposure to air or whole CS from 10 commercial cigarettes (Eighty-Eight Lights, South Korea) for 2 h/day, 5 days/wk for 20 wk. Rats were divided into four groups, including control (CTL; n = 5), smoke-only (SM; n = 5), smoke-plus-celecoxib (SM+Cx; n = 5), and celecoxib-only (Cx; n = 5).
animals. Celecoxib (Celebrex, Pfizer) was orally administered (25 mg/kg) to the SM/H11001 Cx and Cx groups once a day for 20 wk (starting 1 day before CS exposure).

Cell culture and transfection into RAW 264.7 cells by electroporation. RAW 264.7 macrophage cells (American Type Culture Collection, Rockville, MD) were cultured in DMEM supplemented with 10% FCS, 100 U/ml streptomycin, and 2 mM glutamine at 37ÆC in a 5% CO2 humidified incubator. Cells were plated at a density of 3 \times 10^5 cells/60-mm dish. COX-2 siRNA (Santa Cruz Biotechnology) was used for COX-2 RNAi knockdown. The transfection of siRNA in cells was performed using MicroPorator (MP-100; Digital Bio Technology, South Korea) according to the manufacturer’s instructions. Transfection efficiency was >80% as assessed by GFP fluorescence. None of the siRNAs exhibited any significant cytotoxicity.

Cell stimulation. RAW 264.7 macrophages were plated at a density of 3 \times 10^5 cells/60-mm dish. The cells were rinsed with fresh medium and stimulated with 0.5 μg/ml LPS (Sigma-Aldrich, St. Louis, MO) for 3 h in the presence or absence of different concentrations of celecoxib (10^{-9} or 10^{-7} μM), indomethacin (10 or 50 μM, Sigma), and diclofenac (50 or 100 μM, Sigma), which were administered 60 min before the addition of LPS. Celecoxib was dissolved in DMSO. Before the 3-h stimulation with LPS (0.5 μg/ml), the cells were transfected with 8 nM COX-2 siRNA for 24 h.

Tissue preparations. At the end of the 20 wk, the rats were deeply anesthetized with pentobarbital, and blood was collected by cardiac puncture and centrifuged and then stored at -80°C until use. After ligation of the hilum of the right lung, the right lungs were removed and stored at -80°C until use.

Histology. After the right lungs were removed, the rats were perfused with a fixative solution containing 4% paraformaldehyde in 0.1 M PBS (pH 7.0). The left lungs were fixed with the same fixative for 24 h at 4°C. The samples were then processed in preparation for paraffin embedding, and 5-μM-thick sections were cut. Sections were stained with hematoxylin and eosin (H&E), and the slides were evaluated by microscopy.

Quantification of emphysema and inflammation. Emphysema is a structural disorder characterized by destruction of the alveolar walls and enlargement of the alveolar spaces. We quantified the enlargement of alveolar spaces by determining the mean linear intercept (MLI) after the 20 wk of CS exposure using the Image-Pro plus program (Media Cybernetics). The MLI was obtained by dividing the length of a line drawn across the lung section by the total number of

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Fig. 1. Determinations of mean linear intercept (MLI) in lung sections obtained from rats with cigarette smoking (CS)-induced emphysema. A: photomicrographs of H&E-stained lung sections from control (CTL), smoke (SM), smoke+celecoxib (SM+Cx), and celecoxib (Cx) rats. Magnification, ×100. B: morphometric analysis of MLI is presented as means ± SE. aSignificantly different from CTL; csignificantly different from SM+Cx; and dsignificantly different from Cx. Significance P < 0.05 by ANOVA.

Fig. 2. Effects of celecoxib on airway inflammation in rat lungs with CS-induced emphysema. A: representative H&E-stained lung sections from CTL, SM, SM+Cx, and Cx rats. Magnification, ×100. B: inflammation scores are presented as means ± SE of 5 rats/group. Celecoxib decreased CS-induced peribronchial and perivascular inflammation. aSignificantly different from CTL; csignificantly different from SM+Cx; and dsignificantly different from Cx. Significance = P < 0.05 by ANOVA. Arrow indicates the inflammatory area.
The inflammation was quantified using a double-blind screen with two independent investigators. The degrees of peribronchial and perivascular inflammation were evaluated using a subjective scale that ranged from 0 to 3, as described elsewhere (27). Total lung inflammation was defined as the average of the peribronchial and perivascular inflammation scores. Images of these sections were examined using the Image-Pro Plus program (Media Cybernetics), which was calibrated using a reference measurement slide, to perform quantitative and semiquantitative analyses.

**Western blot analysis.** Total right lung and cellular extracts, cytosolic fractions, and nuclear fractions were prepared according to Müller et al. (21). The protein concentration of each lysate was determined using a bicinchoninic acid (BCA) kit (Pierce) according to the manufacturer’s protocol, using BSA as a standard. Equal amounts of protein (30 μg) were separated by SDS-PAGE and transferred to nitrocellulose membranes. The membranes were washed in Tris-buffered saline containing 0.5% Tween 20 (TBST) and incubated with the following TBST-diluted primary antibodies: rabbit anti-iNOS (Chemicon International); rabbit anti-COX-2 (dilution 1:1,000, Cayman Chemical); mouse anti-phospho-IκB (dilution 1:1,000, Santa Cruz Biotechnology); rabbit anti-NF-κB p105/p50 (dilution 1:1,000, Abcam). The samples were then incubated with their corresponding secondary antibodies. The enhanced chemiluminescence Western blot analysis system (Amersham Pharmacia Biotech) was used for detection. To determine the relative amounts of protein in each lane, the levels of α-tubulin were used as an internal control.

**Assay for nitrite production.** NO was measured using its stable oxidative metabolite, nitrite, as previously described (8). Each serum was mixed with an equal volume of Griess reagent (0.1% naphthylethenediamine dihydrochloride and 1% sulfanilamide in 5% phosphoric acid). The absorbance was measured at 550 nm, and the concentration of nitrite was determined using a standard curve generated using sodium nitrite standards.

**Statistical analysis.** Values are expressed as means ± SE. Differences between the groups (i.e., CTL, SM, SM+Cx, and Cx) were determined using ANOVA, followed by a Student-Newman-Keuls test for all pairwise multiple comparisons. *P* values < 0.05 were considered statistically significant.

**RESULTS**

**Effects of celecoxib on the MLI in rat lungs with CS-induced emphysema.** We measured the MLI by examining the CS-induced destruction of alveolar architecture within H&E-stained lung sections (Fig. 1). Compared with the normal alveolar structure, chronic exposure to CS for 20 wk induced

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**Fig. 3.** Effects of celecoxib on CD68 immunoreactivity in rat lungs with CS-induced emphysema. Representative CD68-specific immunostaining of lung sections from CTL, SM, SM+Cx, and negative control (Negative). CD68 immunoreactivity was localized to macrophages. Magnification, ×200. Arrows indicate macrophages.
emphysema, leading to the enlargement of air spaces (Fig. 1A). However, celecoxib significantly decreased MLI in CS-treated rats with celecoxib treatment (Fig. 1B).

Effects of celecoxib on airway inflammation in rat lungs with CS-induced emphysema. In response to CS exposure, infiltrating inflammatory cells contribute to the structural destruction of lung tissue. To evaluate airway inflammation, we stained lung sections with H&E and calculated the resulting inflammation scores (Fig. 2). Marked peribronchial and perivascular inflammatory infiltrates were observed in the lung tissue obtained from rats with CS-induced emphysema, but not in control rats (Fig. 2A). Peribronchial, perivascular, and total lung inflammation scores were significantly higher in CS-treated rats than in control rats (Fig. 2B). The higher peribronchial and perivascular lung inflammation scores were moderately reduced with celecoxib treatment, demonstrating that celecoxib inhibits inflammation of the airways. To confirm these findings, we performed immunohistochemistry for the macrophage marker, CD68 (Fig. 3). CD68-immunostained macrophage cells were observed in the lung sections obtained from each group. Importantly, there were many more CD68-stained macrophages in the alveoli of emphysematous-like lungs isolated from SM-treated rats. However, there was no significant difference in the number of CD68-stained macrophages between SM+Cx-treated and SM-treated rats.

Celecoxib inhibits nitrite production and iNOS expression in rat lungs with CS-induced emphysema. NO is a critical signaling molecule produced by iNOS at inflammatory sites. In this study, we investigated the effects of celecoxib on NO production and iNOS expression in CS-damaged rat lungs (Fig. 4). As shown in Fig. 4A, the nitrite level (equivalent to the NO level) was markedly elevated in the serum from rats with CS-induced emphysema (P = 0.003). Our data revealed that celecoxib significantly inhibited CS-induced NO production (P = 0.001). To further evaluate this inhibition of NO production, we performed Western blot analyses for iNOS (Fig. 4B). Our results showed that dietary celecoxib decreased the expression of iNOS protein in tissue from lungs damaged by CS-induced emphysema.

Celecoxib inhibits COX-2 expression and PGE2 production in rat lungs with CS-induced emphysema. NO directly activates COX-2 protein expression; thus, we investigated the effects of celecoxib on CS-induced COX-2 expression and PGE2 production in rat lungs (Fig. 5). Western blot analyses revealed that dietary celecoxib decreased COX-2 expression in rat lungs damaged by CS-induced emphysema (Fig. 5, A and B). Immunohistochemical evaluations of lungs with CS-induced emphysema revealed higher COX-2 expression in alveolar macrophages and bronchial epithelial cells (Fig. 5C). However, COX-2 immunoreactivity in alveolar macrophages was reduced with celecoxib treatment. We next assessed the production of PGE2, a major product of the enzymatic reaction catalyzed by COX-2 (Fig. 5D). Figure 5D illustrates that celecoxib markedly suppresses PGE2 production in CS-induced lung sections.

Celecoxib inhibits phospho-IkBa and NF-κB expression in rat lungs with CS-induced emphysema. The nuclear translocation of NF-κB is preceded by the phosphorylation-induced ubiquitination and proteolytic degradation of IkB. Hence, we performed Western blot analyses to assess phospho-IkBa (p-IkBα) expression in cytosolic fractions (which correlates to the degradation of IkBα), as well as NF-κB (p65) expression in the cytosolic and nuclear fractions of rat lungs (Fig. 6). Our results showed that the phosphorylation, as well as the CS-induced degradation, of IkB was inhibited by celecoxib treatment (Fig. 6A). We further examined the expression of the p65 subunit of NF-κB in the cytosolic and nuclear extracts from each experimental lung. Celecoxib inhibited NF-κB nuclear translocation (Fig. 6B). These results demonstrate that celecoxib attenuates the CS-induced proinflammatory response by regulating the NF-κB pathway.

Celecoxib inhibits LPS-induced expression of COX-2 and NF-κB translocation in RAW 264.7 macrophages. We analyzed celecoxib-mediated regulation of NF-κB translocation and COX-2 expression in LPS-stimulated RAW 264.7 macrophages. As shown in Fig. 7, A and B, celecoxib (10⁻⁷ μM) inhibited LPS-induced translocation of NF-κB expression and COX-2 expression. To further determine the inhibition of NF-κB-mediated COX-2 expression, we examined the effect of indomethacin and diclofenac on LPS-stimulated NF-κB-dependent COX-2 expression (Fig. 7, C–E). Indomethacin is a more potent inhibitor of COX-1 than COX-2. We confirmed that indomethacin did not translocate NF-κB from cytoplasm to nucleus (Fig. 7C). Diclofenac is an equipotent inhibitor of COX-1 and COX-2 in intact cells. In contrast to indomethacin’s effect, we...
found that diclofenac (100 μM) inhibits the LPS-induced translocation of NF-κB into the nucleus and COX-2 expression in RAW 264.7 cells (Fig. 7, D and E).

COX-2 siRNA inhibits LPS-induced expression of COX-2 and NF-κB translocation in RAW 264.7 macrophages. We demonstrated that celecoxib’s ability to downregulate NF-κB activation is related to its ability to inhibit COX-2 expression by performing an experiment using COX-2 siRNA. Although COX-2 siRNA did not induce the nuclear translocation of NF-κB in RAW 264.7 cells, celecoxib inhibited LPS-induced translocation of NF-κB expression (Fig. 8A). In addition, COX-2 siRNA inhibits LPS-induced COX-2 expression (Fig. 8B).

**DISCUSSION**

Chronic CS exposure is the main risk factor for the development of COPD, a disease that is characterized by pulmonary inflammation and remodeling of alveolar spaces. Before our study, the biological mechanisms of celecoxib treatment in patients with pulmonary diseases were unclear. In this study, we demonstrate that celecoxib attenuates long-term CS-induced inflammation in rat lungs. Specifically, celecoxib reduces lung alveolar destruction, inflammatory infiltration, serum NO production, and the CS-mediated induction of iNOS, COX-2, PGE2, p-IκBα, and NF-κB in rat lung tissue. In addition, celecoxib inhibits LPS-induced NF-κB activation and COX-2 expression in COX-2-sufficient or -deficient RAW 264.7 macrophages. These results indicate a role for this anti-inflammatory pathway in the lung response of lung tissue to CS-induced inflammation and pulmonary emphysema.

CS activates macrophages and the production of several inflammatory mediators that promote the recruitment of inflammatory cells (41). Together with released inflammatory mediators...
cytokines, these processes result in failure of repair mechanisms, leading to the alveolar destruction associated with emphysema (11). Matrix metalloproteinases (MMPs) are implicated in the development of emphysema. Alveolar macrophages from COPD patients show an enhanced release of MMP9 (29). Interestingly, we show that CS-induced destruction of alveolar architecture is associated with increased MLI, resulting in the enlargement of air spaces. Also, the destruction of respiratory bronchioles coincided with CS-induced pulmonary inflammation (10). Heckman and Dalbey (9) observed perivascular and bronchiolar inflammation in rats exposed to smoke. In staphylococcal enterotoxin type A-treated rats, celecoxib markedly reduced lung neutrophil influx and TNFα and nitrite levels in bronchoalveolar (BAL) fluid (5). Celecoxib inhibits PGE2 and IL-10 production in alveolar macrophages isolated from heavily active smokers (15). Our present data show that the oral administration of celecoxib inhibits the increased inflammation and the destruction of alveolar architecture. Therefore, we indicate that celecoxib inhibits CS-induced pulmonary emphysema and inflammation.

Celecoxib is commonly used to alleviate inflammation and pain, particularly joint pain (7, 17). The risk of adverse cardiovascular events appears to be lower among users of celecoxib than among users of coxibs and other classic NSAIDs (33, 34). Traditional NSAIDs act primarily by inhibiting COXs (40). Indomethacin inhibited tachyzoite-induced PGE2 production and COX-2 mRNA expression in macrophages, but it had no significant effect on COX-2 protein expression (23). It was 60 times more potent against COX-1 than COX-2 (19). Diclofenac diminished NF-κB-binding activity and COX-2 expression of IL-1β-stimulated human synoviocytes (1). However, a recent systemic study claimed that diclofenac has the highest cardiovascular risk score of the nonselective NSAIDs (18). Otherwise, celecoxib has exhibited anti-inflammatory activity in several models of human disease. For example, celecoxib inhibited NO production in chondrocytes obtained from ligament-damaged osteoarthritic rat joints (32) and decreased lung inflammation and PGE2 production in a murine model of butylated hydroxytoluene (BHT)-induced lung injury (12). Furthermore, dietary celecoxib limited macrophage infiltration, abrogated PGE2 production, and reduced particulate

![Fig. 7. Effects of celecoxib or other nonsteroidal anti-inflammatory drugs on LPS-induced NF-κB translocation and COX-2 expression in RAW 264.7 macrophages. A and B: cells were incubated with different concentrations (10^-9 or 10^-7 μM) of celecoxib for 60 min before the addition of LPS (0.5 μg/ml) for 3 h. Cell lysates were subjected to Western blot analysis using NF-κB or COX-2 antibodies. C: cells were incubated with different concentrations (10 or 50 μM) of indomethacin (Indo) for 60 min before the addition of LPS (0.5 μg/ml) for 3 h. Cell lysates were subjected to Western blot analysis using NF-κB antibody. D and E: cells were incubated with different concentrations (50 or 100 μM) of diclofenac (diclo) for 60 min before the addition of LPS (0.5 μg/ml) for 3 h. Cell lysates were subjected to Western blot analysis using NF-κB or COX-2 antibodies. The data are representative of at least 2 independent experiments.](http://ajplung.physiology.org/)

![Fig. 8. Effects of celecoxib on LPS-induced NF-κB translocation and COX-2 expression in COX-2 siRNA transfected RAW 264.7 macrophages. A and B: cells were transfected for 24 h before with 8 nM COX-2 siRNA and incubated with different concentrations (10^-9 or 10^-7 μM) of celecoxib for 60 min before the addition of LPS (0.5 μg/ml) for 3 h. Cell lysates were subjected to Western blot analysis using COX-2 or NF-κB antibodies. The data are representative of at least 2 independent experiments.](http://ajplung.physiology.org/)
5-lipoxygenase (LOX) expression. Oxidative stress and the imbalance of host defense mechanisms have been implicated in the pathogenesis of COPD (24). Redox-sensitive transcription factors, such as NF-κB and activator protein (AP)-1, are activated in epithelial cells and inflammatory cells during oxidative stress, thereby upregulating a number of anti- and proinflammatory genes, including those encoding HO-1 and iNOS (25). The expression of iNOS in murine macrophages depends on NF-κB activation (3). Our results indicate that celecoxib likely inhibits iNOS and COX-2 expression by suppressing NF-κB activation. This finding is consistent with previous reports that NF-κB-responsive elements are present within the promoter regions of the iNOS and COX-2 genes (28, 42).

Furthermore, we found that p50 levels decreased in the nucleus in response to celecoxib treatment, indicating that celecoxib blocks the CS-induced activation of NF-κB. Our results demonstrate that celecoxib itself did not activate NF-κB, but rather abolished the CS-mediated induction of NF-κB activation. This study indicates that celecoxib suppresses the CS-induced expression of NF-κB-regulated iNOS and COX-2. Our results are consistent with a recent report showing that celecoxib inhibits NF-κB production by suppressing the activation of IkBα kinase in human non-small cell lung carcinoma (31). In addition, we found that celecoxib inhibited NF-κB translocation and COX-2 expression in COX-2-sufficient or -deficient RAW 264.7 macrophages. A previous study showed that ECM-induced MMP-9 expression in RAW 264.7 macrophages is inhibited by celecoxib or siRNA-mediated reduction of COX-2 expression (22). Wang et al. (39) demonstrated that COX-2-specific siRNA had no blocking effect on p38 MAPK, ERK, and NF-κB pathway in LPS-induced human nasal epithelia (HNE) cells. After COX-2-specific siRNA was transfected into HNE cells, the LPS-induced COX-2 expression was blocked, and PGE₂ release was inhibited. However, no change of the LPS-induced protein levels of p-p38MAPK, p-ERK, NF-κBp50, and NF-κBp65 could be detected. This study was in accordance with our results. Although COX-2 siRNA inhibits LPS-induced COX-2 expression in RAW 264.7 macrophages, translocation of NF-κB to nucleus was not done by COX-2 siRNA transfection. However, we found that celecoxib inhibits translocation of NF-κB to nucleus in response to celecoxib treatment, indicating that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection. However, we found that celecoxib blocks the CS-induced activation of NF-κB to nucleus in COX-2 siRNA transfection.


