Autocrine/Paracrine Prostaglandin E2 Production by Non-small Cell Lung Cancer Cells Regulates Matrix Metalloproteinase-2 and CD44 in Cyclooxygenase-2-dependent Invasion*

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Tumor cyclooxygenase-2 (COX-2) expression is known to be associated with enhanced tumor invasiveness. In the present study, we evaluated the importance of the COX-2 product prostaglandin E2 (PGE2) and its signaling through the EP4 receptor in mediating non-small cell lung cancer (NSCLC) invasiveness. Genetic inhibition of tumor COX-2 led to diminished matrix metalloproteinase (MMP)-2, CD44, and EP4 receptor expression and invasion. Treatment of NSCLC cells with exogenous 16,16-dimethylprostaglandin E2 significantly increased EP4 receptor, CD44, and MMP-2 expression and matrix gel invasion. In contrast, anti-PGE2 decreased EP4 receptor, CD44, and MMP-2 expression in NSCLC cells. EP4 receptor signaling was found to be central to this process, because antisense oligonucleotide-mediated inhibition of tumor cell EP4 receptors significantly decreased CD44 expression. In addition, agents that increased intracellular cAMP, as is typical of EP4 receptor signaling, markedly increased CD44 expression. Moreover, MMP-2-AS treatment decreased PGE2-mediated CD44 expression, and CD44-AS treatment decreased MMP-2 expression. Thus, PGE2-mediated effects through EP4 required the parallel induction of both CD44 and MMP-2 expression because genetic inhibition of either MMP-2 or CD44 expression effectively blocked PGE2-mediated invasion in NSCLC. These findings indicate that PGE2 regulates COX-2-dependent, CD44- and MMP-2-mediated invasion in NSCLC in an autocrine/paracrine manner via EP receptor signaling. Thus, blocking PGE2 production or activity by genetic or pharmacological interventions may prove to be beneficial in chemoprevention or treatment of NSCLC.

Cyclooxygenase is the rate-limiting enzyme for the production of prostaglandins and thromboxanes from free arachidonic acid (1). Two isoenzymes of cyclooxygenase (COX) have now been described: a constitutive enzyme COX-1 present in most cells and tissues and an inducible enzyme COX-2 (also referred to as PGH-S2). COX-2 is known to be up-regulated in response to cytokines, growth factors, and other stimuli (1, 2). Mounting evidence documents elevated expression of COX-2 in a variety of malignancies including colon, gastric, esophageal, prostate, pancreatic, breast, and lung carcinomas (3–12). Overexpression of tumor COX-2 may be important in tumor invasion (13, 14), angiogenesis (15–18), resistance to apoptosis (19–21), and suppression of host immunity (19, 20–21). We reported previously that COX-2 is overexpressed in human NSCLC, and the resultant high level PGE2 production mediates dysregulation of host immunity by altering the balance of interleukins 10 and 12 (12). Accordingly, specific inhibition of COX-2 or PGE2 led to significant in vivo tumor reduction in murine lung cancer models (22). Recently, other investigators have expanded on and corroborated these observations, indicating the importance of COX-2 expression in lung cancer (23–28).

Elevated expression of COX-2 has been shown to increase tumor invasiveness and enhance metastatic potential (3, 29). The complex events associated with tumor cell invasion include the active movement of cells across the extracellular matrix and spread to distant organ sites (30). CD44 is a cell surface receptor for hyaluronate, a major glycosaminoglycan component of extracellular matrix. Adhesion to extracellular matrix, a critical initial step in the metastatic process, has been found to be CD44-dependent in several malignancies (31–34). Our previous findings indicate that tumor COX-2 expression is a critical determinant of CD44 expression and invasion in NSCLC (35). In concert with CD44, matrix metalloproteinase (MMP) expression is important for tumor invasion. Cell surface CD44 induces co-clustering of MMPs, thereby promoting MMP activity, tumor invasion, and angiogenesis (31, 36, 37). Our current studies focus on the role of tumor-derived PGE2 in modulating COX-2-dependent NSCLC invasion.

PGE2, produced at heightened levels in COX-2-overexpressing tumor cells, affects target cells through interaction with G-protein-coupled EP receptors of at least four distinct subtypes. In this study, we addressed the pathways whereby autocrine/paracrine production of PGE2 could impact tumor phenotype via EP receptor signaling in NSCLC.

Here, we report that antibody-mediated blockade of tumor-derived PGE2 decreased both CD44 and MMP-2 expression as well as invasion. In addition, exposure of NSCLC cells to 16,16-

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‡ The abbreviations used are: COX, cyclooxygenase; MMP, matrix metalloproteinase; NSCLC, non-small cell lung cancer; PGE2, prostaglandin E2; IBMX, 3-isobutyl-1-methylxanthine; dmPGE2, 16,16-dimethyl-prostaglandin E2; IL, interleukin; SFM, serum-free medium.

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dimethyl-prostaglandin E2 (dmPGE2) up-regulated CD44, EP4 receptor, and MMP-2 expression and potently enhanced invasion. The parallel increase in both CD44 and MMP-2 expression appears to be required to mediate invasiveness; genetic inhibition of either CD44 or MMP-2 expression abrogated PGE2-mediated invasion. This is the first report indicating an important autocrine/paracrine role of PGE2 in the regulation of CD44 and MMP-2-dependent invasion in human NSCLC.

**EXPERIMENTAL PROCEDURES**

Reagents—Forskolin, 3-isobutyl-1-methylxanthine (IBMX), dibutyryl cAMP, dibutyryl cGMP, and cholera toxin were obtained from Sigma. NS-398 (N-(2-cyclohexyloxy-4 nitrophenyl) methasulfonamide) and dmPGE2 were purchased from Cayman Chemicals (Ann Arbor, MI). Anti-PGE2 (monoclonal antibody 2B5) and isotype-matched control mouse IgG1 (MOPC21) were generously provided by Pharmacia, MI. Anti-PGE2 (monoclonal antibody 2B5) and isotype-matched control mouse IgG1 (MOPC21) were generously provided by Pharmacia, MI. Anti-PGE2 significantly reduced the capacity of IL-1β to induce CD44 (*, p < 0.05). The data represent the mean ± S.D. of triplicate determinations in one representative experiment of three separate experiments.

**Flow Cytometry Analysis**—For the analysis of CD44 and EP4 receptor expression, the cells from each treatment group were harvested and labeled with either fluorescein isothiocyanate-conjugated goat anti-rabbit serum (Jackson ImmunoResearch Laboratory, West Grove, PA). The fluorescein isothiocyanate-labeled cells were then analyzed by flow cytometry using a Becton Dickinson FACScan. Controls included cells stained with fluorescein isothiocyanate-conjugated mouse IgG1 (Dako Corp.) or with secondary antibody alone.

**Gelatin Zymography**—Serum-free tumor supernatants were analyzed for the level of MMP-2 using SDS-polyacrylamide gel zymography. Briefly, 5 × 10^5 cells from each group were plated in six-well plates. Complete medium was replaced with serum-free medium after 24 h. Following incubation at 37 °C for 24 h, the serum-free medium from each well was collected and analyzed by 10% zymogram-ready gels prepared according to the manufacturer's protocol. Following electrophoresis, the gels were soaked in 2.5% Triton X-100 on a shaker for 1 h, changing the solution after 30 min to eliminate SDS. After overnight incubation in zymogen activation buffer (50 mM Tris-Cl, pH 7.5), containing 5 mM CaCl₂, 200 mM NaCl and 0.02% Brij-35 at 37 °C, the gels were rinsed in distilled water and stained for 2–3 h with Phastgel Blue R stain as previously described (38).
Invasion Assay—The membrane invasion assay was performed in Matrigel-coated invasion chambers (Becton Dickinson Labware, Franklin Lakes, NJ) as previously described (35). Control and COX-2 transfectants were cultured in RPMI 1640 supplemented with 10% fetal bovine serum. Tumor cell-conditioned medium was generated as previously described (35) and was added in the lower chamber as a chemottractant. 5 × 10⁴ cells were plated in the upper chamber in both control and test conditions. Following an 18-h incubation at 37 °C in a humidified 5% CO₂ atmosphere, the cells in the upper chamber and on the Matrigel were mechanically removed with a cotton swab. The cells adherent to the outer surface of the membrane were stained with Diff-Quick stain (Dade Behring Inc., Newark, DE) according to the manufacturer's instructions. The invading cells were examined, counted, and photographed by microscopy (Nikon Labphot-2 Microscope with an attached Spot Digital Camera, A. G. Heinz, Lake Forest, CA) at ×50 magnification. Six fields were counted per filter in each group, and the experiment was repeated five separate times. Medium alone controls showed CD44 expression that was not significantly different from oligonucleotide control values (data not shown).

**CD44, MMP-2, and EP4 Receptor Phosphorothioate Antisense Oligonucleotides—** Human CD44, MMP-2, and EP4 receptor antisense and control phosphorothioate-modified DNA oligonucleotides were synthesized by the Molecular Biology Institute and UCLA Jonsson Comprehensive Cancer Center. The sequence of the CD44-specific antisense oligonucleotides was 5'-TATT TGAAAGCCTAC-3', and that of control oligonucleotides was 5'-TATGTTAAGGACATC-3'. The sequence of the EP4 receptor-specific antisense oligonucleotide was 5'-CACATCTTTCGTCGA-3', and that of control oligonucleotides was 5'-CGTCCCCATACAGCC-3'. The sequence of the MMP-2-specific antisense oligonucleotides was 5'-CACATCTTTCGTCGA-3', and that of control oligonucleotides was 5'-CGTCCCCATACAGCC-3'. Briefly, in all studies, NSCLC cells were cultured to 50% confluence. The regular tissue culture medium was replaced with serum-free medium. For MMP-2 blocking studies, control and MMP-2 phosphorothioate antisense oligonucleotides (5 μM) were added to the wells. Following a 30-h incubation, serum-free medium (SFM) was collected and analyzed for MMP-2 by gelatin zymography. In order to evaluate the role of MMP-2 in PGE2-induced CD44 expression, tumor cells were treated with control and MMP-2 phosphorothioate antisense oligonucleotides (5 μM) for 30 h and were further incubated with dmPGE2 for 3 h. The treated cells were then analyzed for CD44 expression by flow cytometry. For EP4 receptor blocking and CD44 expression studies, control and EP4 phosphorothioate antisense oligonucleotides (2 μM) were added to tumor cells. Following a 48-h incubation, cells were treated with dmPGE2 for 3 h and then analyzed for EP4 receptor and CD44 expression by flow cytometry. For CD44 blocking and MMP-2 expression studies, control and CD44 phosphorothioate antisense oligonucleotides (4 μM) were added to tumor cells. Following a 72-h incubation, cells were incubated with dmPGE2 for 3 h, and SFM was collected and analyzed for MMP-2 by gelatin zymography.

**RESULTS AND DISCUSSION**

Experimental data support the relationship between COX-2, its synthesized product PGE2, and neoplastic transformation of epithelial cells (39, 40). Transcription of COX-2 is constitutively up-regulated in several different malignancies including lung cancer (4–9, 11, 12). Our previous studies documented a tumor COX-2-dependent regulation of CD44 and invasion in NSCLC (35). Here, we investigated the pathways by which COX-2 promotes tumor cell invasion. We tested whether the COX-2 enzyme product PGE2 was responsible, in an autocrine/paracrine manner, for mediating the increase in CD44 and MMP-2. In order to determine the effect of PGE2 on CD44 expression, NSCLC cells were treated with dmPGE2. A dose-dependent increase in NSCLC cell CD44 expression was detected by flow cytometry analysis (Fig. 1A). IL-1β, a potent inducer of COX-2, was found to increase CD44 expression in a PGE2-dependent manner (Fig. 1B). These findings suggest that the induction of CD44 expression in NSCLC is dependent, at least in part, on tumor-derived PGE2.

PGE2 elicits its autocrine/paracrine effects on target cells through interaction with prostaglandin E series receptors of four distinct subtypes, designated EP1, EP2, EP3, and EP4.

**TABLE I**

| Experimental conditions | Mean fluorescence intensity | Control oligonucleotides | EP4-antisense oligonucleotides |
|-------------------------|----------------------------|--------------------------|-------------------------------|
| A549-vector             | 87.5 ± 0.7                 | 59 ± 1.4*                |
| A549-vector + dmPGE2    | 181.5 ± 4.9                | 65.5 ± 7.7*              |
| A549-sense              | 138 ± 4.9                  | 49 ± 4.2*                |
| H157-vector             | 57.5 ± 11                  | 45 ± 0.8*                |
| H157-vector + dmPGE2    | 156 ± 1.4                  | 58.5 ± 0.7*              |
| H157-sense              | 488 ± 4.9                  | 255 ± 5.8*               |

* p < 0.01 compared with control oligonucleotide.

† p < 0.05 compared with control oligonucleotide.
EP1 causes influx of Ca$^{2+}$ and activation of protein kinase C; receptors EP2 and EP4 activate adenylate cyclase, which increases cellular cyclic AMP levels and activates protein kinase A; and EP3 signals primarily through an inhibitory G protein to decrease intracellular cyclic AMP levels (41).

PGE2 has the capacity to bind EP2 and/or EP4 receptors, thereby increasing intracellular cAMP, which in turn activates protein kinase C and activation of protein kinase C; whereas significantly fewer cells invaded in MMP-2 antisense oligonucleotide-treated cells ($p < 0.05$). Similarly, significantly fewer cells invaded in MMP-2 antisense oligonucleotide-treated cells ($p < 0.05$).

The roles of the different prostaglandin receptors, their divergent intracellular signaling pathways, and their target genes involved in mediating the effects of PGE2 on normal or neoplastic cells remain to be fully elucidated. Based on previous studies implicating EP4 receptor signaling in PGE2-mediated, G-coupled protein-dependent events in human cancer cells (47, 48), we evaluated the regulation of EP4 in response to increased COX-2 and PGE2. Overexpression of COX-2 increased tumor cell EP4 receptor expression and thus may increase sensitivity to the autocrine and paracrine effects of PGE2 itself. The results presented here indicate an increased expression of EP4 receptor in COX-2-overexpressing (COX-2-S) cells and a relative decreased expression in COX-2 antisense (COX-2-AS) cells compared with vector-transduced controls (Fig. 2A). We next sought to determine whether PGE2 itself played a role in the COX-2-mediated regulation of EP4 receptor expression. Whereas PGE2 induced EP4 receptor expression, anti-PGE2 antibody significantly down-regulated constitutive A549 EP4 receptor expression (Fig. 2B). This suggests that the COX-2-mediated increase in EP4 receptor expression involves autocrine signaling by tumor-derived PGE2 (Fig. 2B). In addition, these findings suggest that COX-2-overexpressing lung cancer cells may be highly dependent on PGE2 for autocrine regulation of EP4 receptor expression.
cancer cells not only produce increased PGE2 but also have heightened sensitivity to PGE2-mediated effects due to overexpression of the EP4 receptor (Fig. 2B). These data are consistent with the previous reports indicating that PGE2 may regulate EP receptor expression in certain cell types (49). The fact that anti-PGE2 monoclonal antibody did not significantly decrease constitutive EP4 receptor expression in H157 cells suggests that other COX-2-dependent mediators may be operative in maintaining EP4 receptor expression in these cells (Fig. 2B). Further studies will be required to define these additional products.

In order to determine the role of EP4 receptor-dependent signaling in regulating CD44 expression in COX-2-S cells, specific inhibition of EP4 receptor expression was accomplished with antisense oligonucleotides. As anticipated, EP4 receptor-specific antisense oligonucleotides used in these studies significantly blocked PGE2-mediated elevated expression of the EP4 receptor in NSCLC cells (data not shown). The PGE2-mediated up-regulation of CD44 expression in NSCLC cells and the constitutive high level expression of CD44 in COX-2-S cells were significantly decreased by specific genetic inhibition of the EP4 receptor (Table I). Thus, EP4 receptor-dependent signaling plays a direct role in PGE2-mediated CD44 expression in NSCLC cells as well as the constitutively elevated levels of CD44 seen in COX-2-S cells.

Degradation of extracellular matrix and penetration of the basement membrane are required for tumor invasion and metastasis (50). The MMP family is a group of proteolytic enzymes that have been associated with invasion and metastasis (50, 51). The major component of the basement membrane, type IV collagen, serves as a substrate for MMP-2 and MMP-9 (72- and 92-kDa type IV collagenases, respectively). Several reports have correlated neoplastic epithelial invasion and metastasis with overexpression of these MMPs (52). We focused on MMP expression because of reports indicating an increase in MMP-2 expression and metastatic potential in COX-2-overexpressing colon cancer cells (29) and because of the involvement of MMPs in metastasis of NSCLC (53, 54). Furthermore, CD44 serves to induce co-clustering with MMPs and can therefore promote MMP activity, tumor invasion, and angiogenesis (31, 36). Here we find that the level of MMP-2 is increased in COX-2-overexpressing NSCLC cells but decreased in COX-2 antisense cells (Fig. 3A). Thus, overexpression of tumor COX-2 elevates MMP-2 and facilitates invasion in NSCLC. The addition of anti-PGE2 antibody to COX-2-S cells significantly blocked MMP-2 production in NSCLC cells (Fig. 3B), indicating that the autocrine/paracrine influence of PGE2 regulates MMP-2 expression in these cells. Attiga et al. (55) have reported the inhibition of MMP-2 and MMP-9 by COX-2 inhibitors in prostate cancer. Consistent with these previous findings, the treatment of COX-2-overexpressing cells (A549-S) with a COX-2-specific inhibitor showed decreased levels of MMP-2 (Fig. 3C). However, MMP-9 was not regulated in A549 or H157 cell lines (data not shown).

In order to define the pathways responsible for COX-2-dependent induction of MMP-2, we determined the level of tumor MMP-2 in the presence of exogenous PGE2. The addition of PGE2 increased the level of MMP-2 and invasion in NSCLC (Fig. 4, A and B, lower left panel). Decreases in MMP-2 level and invasion were observed when MMP-2-AS oligonucleotides were utilized in PGE2-treated cells (Fig. 4, A and B, lower right panel). Similar results were also obtained in H157-S cells (data not shown). MMP-2-AS oligonucleotides were also shown to block PGE2-mediated CD44 expression in NSCLC cell (Table II). In activated human monocytes, MMPs are known to be regulated through a PGE2-cAMP-dependent pathway (56). More recently, CD44 has been implicated in the regulation of MMPs in human cancer cells (57, 58), which suggests a fundamental role for CD44 in regulating MMP-2 expression and the

| Table II |
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| MPP-2-specific antisense oligonucleotides (oligos) inhibit PGE2-mediated CD44 expression |

| Experimental conditions | Mean fluorescence intensity |
| --- | --- |
| A549-vector | 166 ± 6.3 |
| A549-vector + dmPGE2 | 235 ± 1.4* |
| A549-vector + dmPGE2 + Ctrl. oligos | 225 ± 22.6 |
| A549-vector + dmPGE2 + AS-oligos | 168 ± 2.1* |

* p < 0.001 compared with A549-vector control.

** p < 0.001 compared with control oligonucleotide.
invasive phenotype. Previously, we have reported the inhibition of invasion in COX-2-S cells using anti-CD44 antibody. Here we demonstrate the inhibition of PGE2-mediated expression of MMP-2 and NSCLC cell invasion with CD44-specific antisense oligonucleotides (Fig. 5, A and B, lower right panel). Thus, blocking CD44 expression inhibits the expression of MMP-2 and invasion in NSCLC cells.

Here, for the first time, we document the autocrine/paracrine role of PGE2 in up-regulating the expression of CD44 and MMP-2 in human lung cancer cells. In collaboration with CD44, MMP-2 expression is also responsible for NSCLC cell invasion. Thus, our studies and reports in the literature support the hypothesis that CD44 and MMP-2 act in concert to promote tumor invasion (59, 60). Clear understanding of the regulatory pathways whereby COX-2 overexpression leads to CD44- and MMP-2-dependent invasion in NSCLC may promote the development of specific targeted therapies that are based on the molecular pathogenesis of the disease.

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