Cyclooxygenase-2 expression in human pancreatic adenocarcinomas

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Introduction

Cancer of the exocrine pancreas is the fourth and fifth leading cause of cancer-related deaths in men and women, respectively, in the USA (1). Difficulty in achieving early diagnosis as well as the aggressive nature of this type of cancer contribute to the low survival rate of patients with pancreatic cancer. Since few options exist for the treatment of pancreatic cancer, it is important to identify potential targets for drug therapy. In an effort to gain more insight into pancreatic tumorigenesis, pancreatic tumors have been analyzed at the molecular level to detect genetic lesions. Activating mutations within the K-ras gene have been detected in up to 90% of pancreatic carcinomas, suggesting that activation of the Ras pathway is important in the development of pancreatic cancer (2). Experimental chemotherapeutic strategies for pancreatic cancer patients currently include drugs which target the Ras signal transduction pathway.

Multiple lines of evidence suggest that the enzyme cyclooxygenase (COX), specifically COX-2, may be a promising chemotherapeutic target. For example, epidemiological studies have shown that prolonged use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the risk of colon cancer by 40–50% (3). NSAIDs also inhibit chemically induced colon carcinomas in animal model systems (4). Since NSAIDs are known to inhibit COX, the key enzyme in the conversion of arachidonic acid to prostaglandins and other eicosanoids, these studies imply that COX may play a role in carcinogenesis in addition to its known role in inflammation. Two isoforms of COX, designated COX-1 and COX-2, have been identified. COX-1 is constitutively expressed whereas COX-2 is induced by mitogenic stimuli such as serum, phorbol esters and growth factors (5,6). COX-2 expression has recently been shown to be elevated in several different types of human cancer, suggesting that the presence of COX-2 correlates with cancer development (7–11). Additional studies which directly link COX-2 to carcinogenesis include observations that human colon cancer cells expressing COX-2 acquire increased invasiveness (12) and that COX-2 expressed in intestinal epithelial cells inhibits apoptosis (13). COX-2 expression in colon cancer cells has also been found to promote angiogenesis of cultured endothelial cells by stimulating the production of angiogenic factors (14). Furthermore, direct genetic evidence linking COX-2 to colorectal tumorigenesis was provided by a mouse model for human familial adenomatous polyposis, an inherited condition leading to colorectal cancer; in this system, COX-2 gene knockouts and a specific COX-2 inhibitor were found to reduce the number of intestinal polyps formed (15).

The presence of oncogenic ras has been associated with the induction of COX-2 expression in H-ras-transformed rat intestinal and mammary epithelial cells as well as in non-

Abbreviations: COX, cyclooxygenase; DMSO, dimethylsulfoxide; Erk1/2 MAP kinase, extracellular signal-regulated kinase 1 and 2 mitogen-activated protein kinase; FCS, fetal calf serum; LPS, lipopolysaccharide; MEK, MAP kinase kinase; NSAIDs, non-steroidal anti-inflammatory drugs; NSCLC, non-small cell lung cancer; PGE2, prostaglandin E2; PMA, phorbol 12-myristate 13-acetate.
small cell lung cancer cell lines (NSCLC) (16–18). To our knowledge, the association between oncogenic ras and COX-2 expression has not been explored in vivo. The high frequency of activating mutations within the K-ras gene in pancreatic tumors should enable us to investigate the relationship between oncogenic K-ras and COX-2 expression in vivo. In the present study, we have evaluated COX-2 protein levels in primary human pancreatic adenocarcinomas. We further examined whether COX-2 expression correlated with K-ras mutation status in pancreatic tumors as well as in pancreatic cancer cell lines. In light of our data demonstrating elevated levels of COX-2 protein in primary pancreatic tumors and cell lines, we tested the effect of the COX inhibitors sulindac, indomethacin and NS-398 on cell growth and prostaglandin E₂ production in human pancreatic tumor cell lines.

### Materials and methods

#### Patient samples

Banked tissues were obtained from the Indiana University Tissue Procurement Laboratory and the Cooperative Human Tissue Network, which is funded by the National Cancer Institute. A total of 23 primary human pancreatic cancer specimens were analyzed in this study. Corresponding matched, normal adjacent tissue was obtained from 11 of the patients. The patients were selected on the basis of having no prior chemotherapy. Tissues were frozen in liquid nitrogen within 1 h of surgical removal and subsequently stored at –80°C. Paraffin sections were prepared from a subset of the specimens. All tumor specimens used in this study were examined by a pathologist and classified as primary pancreatic adenocarcinomas. Institutional Review Board approval was obtained for this study.

#### Immunoblots

Frozen tissue was briefly homogenized in RIPA lysis buffer (phosphate-buffered saline, 1% NP40, 0.5% sodium deoxycholate, 0.1% SDS, 1 mM phenylmethylsulfonyl fluoride, 1 mM Na₃VO₄, 20 mM β-glycerophosphate, 1 mM sodium fluoride, 1 μg/ml pepstatin, 20 μg/ml aprotinin and 1 μg/ml leupeptin). Lysates were clarified by centrifugation at 13 000 g for 10 min, followed by boiling in sample buffer. Protein concentrations were determined using the BCA protein assay kit (Pierce). Equivalent amounts of total protein were resolved by SDS-PAGE on 10% gels (Novex) and transferred to Immobilon P membranes (MSI). The blots were probed with the primary antibodies COX-1 (C-20; Santa Cruz Biotechnology), COX-2 (C-20; Santa Cruz Biotechnology), p21ras (pan-ras Ab-3; Oncogene Science), actin (C-11, Santa Cruz Biotechnology), pErf1/2 antibody (New England Biolabs) as well as the phospho-specific actin antibody (Oncogene Research Products) were selected on the basis of having no prior chemotherapy. Tissues were frozen in liquid nitrogen within 1 h of surgical removal and subsequently stored at –80°C. Paraffin sections were prepared from a subset of the specimens. All tumor specimens used in this study were examined by a pathologist and classified as primary pancreatic adenocarcinomas. Institutional Review Board approval was obtained for this study.

#### Immunohistochemistry

Immunohistochemical staining was performed on 5 μm formalin-fixed, paraffin-embedded sections using the avidin–biotin complex technique (19). Primary monoclonal antibody (1:100 dilution; Oxford Biomedical Research Inc., Oxford, MI) was used for evaluation of COX-2 expression. 3,3′-Diaminobenzidine was used as the chromogen and 0.2% methyl green was used as the counterstain. Positive and negative controls were run in parallel and gave appropriate results.

#### K-ras mutation analysis

Genomic DNA was prepared by incubating the tissue in lysis buffer (50 mM Tris, pH 8.0, 100 mM EDTA, 100 mM NaCl, 1% SDS, 0.5 mg/ml proteinase K) overnight at 55°C. RNase (0.1 mg/ml) was added and the incubation was continued for 2 h at 37°C. The sample was then digested with phenol and phenol:chloroform, and ethanol precipitated. K-ras exon 1 of the resuspended genomic DNA (0.5 μg) was amplified by PCR (5′ primer, 5′-ATGACTGAGATATATAACCTGT-3′; 3′ primer, 5′-CTCTATGTTGGAGATATT-3′) (20). K-ras mutation-specific oligonucleotides (Oncogene Research Products) were utilized to detect mutations at K-ras codon 12 in the PCR-amplified products by dot blot hybridization (21). Mutations at K-ras codon 13 were detected by sequencing the PCR amplification products.

### Results

#### COX-2 expression in human pancreatic adenocarcinomas

The expression of COX-2 protein was examined in primary human pancreatic adenocarcinomas (n = 23) and matched normal adjacent pancreatic tissue (n = 11) by immunoblot analysis. A representative immunoblot of lysates prepared from six patients, three with matched normal (N) tissue (sample numbers correspond to those listed in Table I). Lysates were analyzed by immunoblotting with specific COX-2, COX-1, p21ras and actin antibodies as indicated. The positive control (+) for the COX-2 immunoblot is a cell lysate prepared from LPS-treated mouse macrophage cell line Raw 264.7. The negative control (−) is the colon carcinoma cell line HCT 116, which expresses neither COX-1 nor COX-2.

#### Statistical analysis

The presence of a statistically significant elevation of COX-2 protein between cancer specimens and corresponding normal adjacent tissues was determined by the non-parametric signed rank test. A two-way analysis of variance was used to examine the difference in mean percent cell growth between the BxPC-3 and PaCa-2 cell lines in the presence of the COX inhibitors.

### Cell lines

The human pancreatic tumor cell lines (AsPC-1, BxPC-3, Capan-1, Capan-2, HPAF-II, HS766T, PaCa-2 and PANC-1) were obtained from the American Type Culture Collection (ATCC, Rockville, MD) and cultured as recommended. The hamster pancreatic cell lines (D27, D27/K-ras and B12/13) were cultured as described previously (22,23). For the inhibitor studies, BxPC-3 cells were treated with the MAP kinase kinase (MEK) inhibitor PD98059 (40 μM) or dimethylsulfoxide (DMSO) for 10 h. Lysates were prepared and analyzed as described above.

#### Cell growth

Cells were plated in duplicate in 6-well plates in the presence of DMSO, sulindac (Sigma), indomethacin (Sigma) or NS-398 (Biomol). On day 3, cells were trypsinized, stained with trypan blue and counted using a hemocytometer. Cell growth was determined by averaging the cell counts and expressed as a percentage of the number of cells in the DMSO control samples.

#### Prostaglandin E₂ (PGE₂) assay

Cells were plated in 12-well plates. On day 3, the culture medium was aspirated and replaced with 15 μM arachidonic acid in serum-free medium for 1 h prior to assaying the culture supernatant for PGE₂ by enzyme immunoassay (Biotrak; Amersham) as recommended by the manufacturer. The amount of PGE₂ produced was normalized to protein concentration. Intracellular PGE₂ levels were determined by plating cells in 12-well plates in the presence of the COX inhibitors for 24 h followed by cell lysis and quantitation by enzyme immunoassay (Biotrak) as recommended by the manufacturer. For determination of intracellular PGE₂ levels, the cells were not preincubated with arachidonic acid prior to assay.

#### Table I

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**Fig. 1.** Representative immunoblot of pancreatic adenocarcinomas and matched normal tissue. Lysates were prepared from tumor (T) specimens obtained from six patients, three with matched normal (N) tissue (sample numbers correspond to those listed in Table I). Lysates were analyzed by immunoblotting with specific COX-2, COX-1, p21ras and actin antibodies as indicated. The positive control (+) for the COX-2 immunoblot is a cell lysate prepared from LPS-treated mouse macrophage cell line Raw 264.7. The negative control (−) is the colon carcinoma cell line HCT 116, which expresses neither COX-1 nor COX-2.

The expression of COX-2 protein was examined in primary human pancreatic adenocarcinomas (n = 23) and matched normal adjacent pancreatic tissue (n = 11) by immunoblot analysis. A representative immunoblot of lysates prepared from six patients, three with matched normal tissue lysates, is shown in Figure 1. Undetectable levels of COX-2 protein were observed in each of the normal specimens. In contrast, COX-
levels of p21ras and actin expression were found in both the pancreas tumor and normal tissues, although the level of expression was variable and not consistently elevated in the tumor specimens (Figure 1). Similar results were observed in both pancreatic tumor and normal tissues, with LPS, previously shown to induce COX-2 expression (24). To determine if COX-2 expression levels correlated with the K-ras mutation status of the tumors, genomic DNA was isolated from a subset of the tissue specimens and screened for the presence of K-ras mutations at codon 12 by allele-specific hybridization of PCR-amplified K-ras exon 1 products. Specimens which lacked a mutation at codon 12 were subsequently sequenced to search for the presence of K-ras mutations at codon 13 (Table I). All of the normal tissues analyzed were wild-type at codon 12 (GGT = Gly) and codon 13 (GGC = Gly). Of the 13 pancreatic cancer specimens analyzed, one specimen had a mutation at codon 13 whereas 10 samples were mutated at codon 12, corresponding to a K-ras mutation frequency of 85%. There did not appear to be a direct correlation between K-ras mutation and the extent of COX-2 protein expression. For example, some samples expressed high levels of COX-2 protein and possessed a mutation in K-ras (tumor samples 9, 16, and 22), however, other samples which had mutated K-ras expressed little or no COX-2 protein (tumor samples 3, 17, 18, 19, and 21).

Similarly, no direct correlation between the expression of activated K-ras and COX-2 was observed in a panel of human pancreatic adenocarcinoma cell lines with known K-ras mutation status (25,26). Both the frequency and variability in the quantity of COX-2 expressed in the pancreatic tumor cell lines reflected our findings in the primary pancreatic adenocarcinomas. Of the eight human pancreatic tumor cell lines analyzed, only three of the seven cell lines expressing oncogenic K-ras exhibited detectable levels of COX-2 protein (Capan-1, Capan-2 and HPAF-II) (Figure 4A). High levels of COX-2 protein were also observed in the wild-type K-ras-expressing cell line BxPC-3, which displays high levels of Ras-independent Raf activity (26). Treatment of the BxPC-3 cell line with the MEK inhibitor PD98059 significantly reduced the level of active, phosphorylated Erk1/2 suggesting that COX-2 expression is independent of Erk1/2 activation (Figure 4B). Taken together, our results suggest that activation of the Ras pathway is not sufficient to mediate COX-2 up-regulation in pancreatic tumor cells.

We also compared the level of COX-2 expression in three hamster pancreatic cell lines. The D27/K-ras and B12/13 transformed cell lines were derived from the non-malignant hamster pancreatic duct cell line D27 by transfection with oncogenic K-ras or treatment with chemical carcinogens in vitro, respectively (22,23). Although both the D27/K-ras and B12/13 cell lines harbor oncogenic K-ras, only the B12/13 cells showed elevated levels of COX-2 protein compared with the D27 parental line (Figure 4C). These results confirm
Fig. 3. Immunohistochemical staining of pancreatic tumor tissue. Some but not all of the tumor cells are positive for COX-2 (brown reaction product) whereas the surrounding stroma is negative (×200).

our conclusion that Ras activation alone is not sufficient to up-regulate COX-2 expression in pancreatic cancer cells and suggest that additional events which occur following exposure to chemical carcinogens may be required.

To examine whether COX-2 expression could be induced in the human pancreatic cancer cell lines, four cell lines were serum starved and subsequently treated with 10% fetal calf serum (FCS) for various time periods (Figure 4D). In the COX-2-positive BXPC-3 and Capan-1 cell lines, COX-2 was still detectable following serum starvation, although at lower levels than in exponentially growing cells. COX-2 expression was inducible in these cell lines following FCS stimulation. In contrast, COX-2 expression could not be induced by serum treatment in either of the COX-2-negative cell lines, AsPC-1 and PaCa-2. Under these treatment conditions, Erk1/2 is activated (unpublished observations), again demonstrating that Erk1/2 activation is not sufficient to induce COX-2 expression in the COX-2-negative pancreatic tumor cells. We observed similar results upon treating the cell lines with the tumor promoter phorbol 12-myristate 13-acetate (PMA) (unpublished observations).

Treatment of pancreatic tumor cell lines with cyclooxygenase inhibitors

The COX-2-positive human pancreatic tumor cell line BxPC-3 and the COX-2-negative cell line PaCa-2 were treated with the COX inhibitor sulindac, indomethacin, or NS-398. Sulindac and indomethacin are non-selective COX inhibitors, inhibiting both COX-1 and COX-2 (27), whereas NS-398 is a more specific inhibitor of COX-2 (28). The effect of the COX inhibitors on cell growth was measured after 3 days of treatment (Figure 5). All three inhibitors were found to suppress cell growth in both pancreatic tumor cell lines in a dose-dependent manner. However, indomethacin and NS-398 were found to inhibit cell growth to a greater extent in the COX-2-expressing cell line BxPC-3 compared with the PaCa-2 cell line ($P = 0.004$ and $P < 0.001$, respectively). No significant difference in cell growth inhibition was observed between the two cell lines with sulindac treatment ($P = 0.333$).

To evaluate the functional activity of COX-2 in the human pancreatic tumor cell lines, PGE$_2$ production was measured by enzyme immunoassay (Figure 6A). PGE$_2$ production was elevated in the BxPC-3, Capan-1, Capan-2 and HPAF-II cell lines, correlating with the increased level of COX-2 expressed in these cell lines. In contrast, barely detectable levels of PGE$_2$ were detected in the COX-2-negative pancreatic cell lines. To determine the effect of the COX inhibitors on PGE$_2$ production, the COX-2-positive cell line BxPC-3 was incubated with two different concentrations of sulindac (100 and 250 µM), indomethacin (10 and 100 µM) or NS-398 (10 and 50 µM) for 24 h prior to measuring intracellular PGE$_2$ levels (Figure 6B). Intracellular PGE$_2$ rather than PGE$_2$ secreted into the growth medium was measured since intracellular levels should be more sensitive to changes in response to the inhibitor treatments. The two concentrations of the various COX inhibitors were evaluated in the cell growth assays described above (Figure 5), with the higher concentration corresponding to the IC$_{50}$ values of the COX inhibitors. At the lower concentrations, both NS-398 and indomethacin inhibited PGE$_2$ production, by 75 and 95%, respectively; in contrast, sulindac at the lower concentration did not affect PGE$_2$ levels. Nevertheless, all three inhibitors at the higher IC$_{50}$ concentrations substantially suppressed intracellular PGE$_2$ levels, by between 86 and 98%, in the BxPC-3 cell line. These data suggest that the COX inhibitors may exert their effects in the COX-2-positive BxPC-3 cell line at least in part by decreasing PGE$_2$ production. However, in the COX-2-negative cell lines, the effects of the COX inhibitors may be mediated by COX- and PGE$_2$-independent mechanisms.

Discussion

In resting cells, the expression of COX-2 is usually undetectable but can be rapidly induced by mitogenic stimuli as well as
inflammatory agents (5,6,29). Recent studies have shown that COX-2 expression is up-regulated in a variety of human cancers, including colon, lung, gastric, pancreatic and esophageal (7–11). In the present study, we report that elevated levels of COX-2 protein are expressed in human pancreatic tumors compared with barely detectable levels in the matched normal pancreatic tissue, suggesting that increased expression of COX-2 protein correlates with pancreatic tumorigenesis. Our results confirm a recent report demonstrating up-regulation of COX-2 RNA and protein in pancreatic tumors and localization of COX-2 in malignant epithelial cells (11). An earlier study demonstrated that the expression of group II phospholipase A₂, which catalyzes the release of arachidonic acid from membrane phospholipids, was higher in pancreatic ductal adenocarcinomas compared with normal pancreatic tissue (30). In addition, the development of N-nitrosobis(2-oxopropyl)-amine-initiated pancreatic tumors in hamsters was inhibited by the administration of two prostaglandin synthesis inhibitors, phenylbutazone and indomethacin (31). Together with our observations in vivo and in vitro, these studies suggest that increased prostaglandin production due to increased expression of COX-2 may be an important event in the multi-step progression towards pancreatic tumor formation.

Recent studies have suggested that Ras activation may induce COX-2 expression in several systems. Activated, oncogenic H-ras was inducibly expressed in Rat-1 fibroblasts with a concomitant increase in COX-2 expression as well as PGE₂ production (32). In this particular cell line, a specific MEK inhibitor, PD98059, was found to suppress COX-2 induction by oncogenic ras, suggesting that Erk1/2 activation is required for Ras-dependent induction of COX-2. Similarly, elevated levels of COX-2 as well as PGE₂ were detected in ras-transformed mammary epithelial cells (C57/MG) cells (17). In human NSCLC cell lines expressing oncogenic K-ras, increased PGE₂ production was mediated by constitutively high expression of cytosolic phospholipase A₂ and COX-2 compared with NSCLC lines without ras mutations (18). In the present study, we addressed the question of whether the expression of oncogenic K-ras correlated with increased COX-2 expression in primary human pancreatic adenocarcinomas. We found that the presence of a mutation at codon 12 or 13 in the K-ras gene did not correlate with the expression of COX-2.
of detectable levels of COX-2 protein. A possible explanation for the lack of COX-2 expression in a subset of the tumors with oncogenic \( ras \) is that Erk1/2 activity may be downregulated in pancreatic carcinomas (26). Moreover, even in the two pancreatic tumor samples which did show elevated levels of activated Erk1/2 (samples 4 and 21; data not shown), only low levels of COX-2 were detected in the present study, suggesting that Erk1/2 activation alone is not sufficient to induce COX-2 expression. These findings suggest that within the tumor environment, the presence of oncogenic \( K-ras \) does not directly result in increased COX-2 expression in pancreatic cancer.

Similar conclusions were also reached upon analysis of pancreatic cancer cell lines, which were examined since they represent a homogeneous population of cells as opposed to primary tumor tissue, which is heterogeneous. Despite activating \( K-ras \) mutations in seven of the eight lines, only three of the lines with mutated \( K-ras \) expressed detectable amounts of COX-2 protein. COX-2 expression was also elevated in the wild-type \( K-ras \) BxPC-3 cell line, which possesses high levels of active Raf (26). COX-2 was concomitantly expressed in the four COX-2-positive cell lines; in contrast, COX-2 expression could not be induced by serum or PMA in the COX-2-negative cell lines, suggesting that COX-2 expression is blocked in these cells. COX-2 expression in the BxPC-3 cell line was not reduced following treatment with the MEK inhibitor PD98059, suggesting that COX-2 induction is independent of Ras pathway activation in this cell line. Differential expression of COX-2 protein in the transformed hamster pancreatic cell lines generated by either transfection with oncogenic \( ras \) or treatment with chemical carcinogens further demonstrated that Ras activation does not appear to be sufficient to mediate the induction of COX-2 expression. Activation of other signaling pathways in addition to Ras may cooperate to determine the extent of COX-2 expression in cancer cells. Such pathways may include the p38 mitogen-activated protein kinase which has been reported to regulate the induction of COX-2 in LPS-treated human monocytes (33). Furthermore, in human vascular endothelial cells, the transcription factor NF-\( \kappa B \) p65 was found to mediate the induction of COX-2 in response to hypoxia (34). Thus, the induction of COX-2 expression appears to be mediated by multiple signaling pathways. The specific pathway(s) activated may depend upon the cell type as well.
PGE2 production. The BxPC-3 cell line was incubated with DMSO or two SD from two independent experiments. (B) was normalized to protein concentration. Results presented are the means of independent experiments.

Following incubation of exponentially growing cells with 15 µM arachidonic acid in serum-free medium for 1 h, PGE2 levels in the culture supernatant were determined by enzyme immunoassay. PGE2 production was normalized to protein concentration. Results presented are the means ± SD from two independent experiments. (B) Effect of COX inhibitors on PGE2 production. The BxPC-3 cell line was incubated with DMSO or two different concentrations of COX inhibitors (100 µM sulindac, 10 µM indomethacin and 10 µM NS-398, indicated by the black bars; 250 µM sulindac, 100 µM indomethacin and 50 µM NS-398, indicated by the stippled bars) for 24 h prior to cell lysis and measurement of intracellular PGE2 by enzyme immunoassay. The percent inhibition of PGE2 by the COX inhibitors is indicated. The data are representative of at least two independent experiments.

as the stimulus. Further experiments will be required to delineate which signaling pathways are functional in pancreatic tumor cells. Cell growth was inhibited by treatment with the COX inhibitors sulindac, indomethacin and NS-398 in both COX-2-positive (BxPC-3) and COX-2-negative (PaCa-2) cell lines. However, the cell line BxPC-3 was significantly more sensitive to growth inhibition by indomethacin and NS-398 compared with the PaCa-2 cell line, suggesting that these two compounds may be more selective for COX-2-expressing cells than sulindac. Furthermore, in the BxPC-3 cell line, the COX inhibitors at IC50 concentrations substantially decreased intracellular PGE2 levels. No PGE2 was detectable in the non-COX-2-expressing cell lines. These data suggest that the COX inhibitors exert their inhibitory effects by both COX/PGE2-dependent and -independent pathways in pancreatic tumor cell lines. NS-398 has been previously shown to inhibit cell proliferation by inducing apoptosis in a COX-2-independent fashion (35). Similarly, sulindac sulfone, a metabolite of sulindac which does not inhibit COX activity, was found to inhibit colon carcinogenesis in a rat model without decreasing prostaglandin levels (36). Furthermore, in COX null embryo fibroblasts, transformation as well as the antiproliferative and antineoplastic actions of NSAIDs were recently shown to be independent of COX expression (37).

The detection of elevated levels of COX-2 in a variety of human cancers combined with the chemopreventative effect of NSAIDs in colon cancer demonstrate that COX-2 may be an important participant in carcinogenesis. The reported biological consequences of COX-2 up-regulation include inhibition of apoptosis (13), increased metastatic potential (12) and promotion of angiogenesis (14). These events may contribute to cell transformation and tumor progression. We report that COX-2 expression was noticeably elevated in 55% of the patient pancreatic tumor samples analyzed, identifying COX-2 as a promising new target for chemotherapy. Our results demonstrating the ability of COX inhibitors to inhibit pancreatic tumor cell growth and PGE2 production in vitro suggest that NSAIDs may be effective in the treatment of pancreatic cancer patients, for whom few treatment options currently exist. Whether COX-2 expression can be employed as a prognostic or diagnostic tool is also an important issue which remains to be investigated.

Acknowledgements
We thank Ahmad Siar Ayoubi for preparation of the slides for immunohistochemistry. This work was funded by a research grant supplied by Lilly Research Laboratories. Tissue procurement and COX-2 immunoblotting were funded by Smith Kline Beecham.

References

Received July 7, 1999; revised September 7, 1999; accepted October 8, 1999