Profiles of Prostaglandin Biosynthesis in Normal Lung and Tumor Tissue from Lung Cancer Patients

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ABSTRACT

Prostaglandin (PG) biosynthetic profiles from endogenous arachidonic acid were determined by capillary gas chromatography-mass spectrometry in matched fresh normal lung (NL) and lung cancer (LC) tissue fragments obtained from 42 individual LC patients at the time of diagnostic thoracotomy. The histological diagnoses represented were squamous cell carcinoma (N = 20), adenocarcinoma (N = 7), small cell carcinoma (N = 4), mixed cell carcinoma (N = 2), bronchioloalveolar cell carcinoma (N = 2), large cell undifferentiated carcinoma (N = 3), bronchial carcinoma (N = 1), and metastatic tumors (N = 3). When PG biosynthesis was determined in NL tissue separately, low mean levels of PGE2 and PGF2α (2-7 pmol/mg protein/15 min), intermediate levels of PGD2 and 6-keto-PGF1α (6KPGF1α) (2-7 pmol/mg protein/15 min), and high levels of thromboxane B2 (TXB2) (>7 pmol/mg protein/15 min) were observed. There was no particular correlation with cigarette smoking history and PG biosynthesis in NL. When PG production in LC tissue was evaluated separately, high levels of PGE2, PGF2α, and 6KPGF1α, as well as TXB2, and low levels of PGD2 were noted. In addition, LC tissue from cigarette smokers demonstrated elevated levels of PGE2, 6KPGF1α, and TXB2 when compared to current nonsmokers with LC (P < 0.05 in all instances). Simultaneous comparison of PG production in matched LC and NL tissue from individual patients indicated increased biosynthesis of PGE2 and PGF2α and low levels of PGD2 in LC compared to NL tissue (P < 0.05 in all instances; paired, two-tailed Student’s t test). Individual comparison of PG biosynthesis according to LC histological cell type revealed that PGE2 and PGF2α were consistently elevated in all four common primary LC histological cell types, the only exception being large cell undifferentiated carcinoma. Interestingly, this latter LC histological cell type presented a unique profile with lower levels of PGE2 and PGD2 in LC than in NL tissue (P < 0.05 in both instances). In addition, the biosynthesis of all 5 PGs studied was consistently higher in primary than metastatic adenocarcinomas of the lung (P < 0.05 in all instances). No differences were observed in NL and LC tissue for the major LC histological cell types when PGD2, TXB2, or 6KPGF1α biosyntheses were compared. These findings indicate that the profiles of PG biosynthesis in LC and NL tissue from individual patients may differ substantially. These differences may reflect, in part, contributions to the PG biosynthetic profile unique to malignant cells.

INTRODUCTION

Pulmonary carcinomas are a major cause of adult morbidity and mortality in the United States population (1–5). A more detailed understanding of the biochemistry of human LC2 could contribute to the further development and refinement of better approaches to earlier, more specific diagnoses as well as potentially lead to improvements in the therapeutic intervention and treatment of this disease. Studies characterizing human lung carcinomas according to selected neuroendocrine and cellular properties have provided valuable initial information regarding certain biochemical features of pulmonary tumors, particularly small cell carcinomas (see Refs. 6–9 for review). The PGs and related eicosanoids are important mediators of NL function (10–12) and might also be important in the pathophysiology of certain human LC (13–17). Since the lung is a tissue rich in enzymes that biosynthesize PGs and TX as well as inactivate these compounds (18–23) the biosynthetic capability of lung tumor tissue to synthesize this family of compounds might be useful in the classification of LC and provide a more complete understanding of the role of PG and TX in the pathophysiology of this disease (13–17, 24–49).

There is little information currently available regarding the profiles of 20-carbon fatty acid cyclooxygenase products in either NL or LC tissue. In the present studies, the profiles of five such products synthesized from endogenous arachidonic acid in matched NL and LC tissue from individual patients representing several histological classes of human LC were simultaneously compared.

MATERIALS AND METHODS

Study Subjects. LC and NL tissue were obtained at the time of diagnostic thoracotomy at the Johns Hopkins University School of Medicine from 42 LC patients (23 males and 19 females). A summary of the pertinent clinical information for these patients is provided in Table 1. Ninety-three % (39 of 42) of the subjects had presented initially with primary lung tumors. The histological classification of both primary and metastatic LC is provided in Table 2.

Collection, Preparation, and Incubation of Tissue Fragments. Procedures for tissue collection, preparation for experimentation, and incubation for PG from endogenous precursor in vitro are identical to those described previously (50). Triplicate specimens of biopsy fragments of NL and LC tissues were used for determinations of intersample variations of PG biosynthesis in the tissues studied.

PG Analysis. The profiles of PGF2α, PGD2, PGE2, TXB2, 6KPGF1α, and the 15-keto-13,14-dihydrometabolites of PGE2, PGF2α, 6KPGF1α, synthesized from endogenous arachidonic acid were performed via capillary gas chromatography-mass spectrometry as described previously (50). This method of analysis offers a very high degree of selectivity, sensitivity (detection limits <0.1 pg of individual analyte per injection), and reproducibility.

RESULTS

Reproducibility of PG Measurements in Human Lung Biopsy Fragments

Capillary gas chromatography-mass spectrometry measurements of PG synthesized in biopsy fragments of NL tissue and lung carcinoma tissue have been demonstrated previously to be highly reproducible with coefficients of intrasample variations ranging from 2.2 to 18.5% (50). The cellular heterogeneity of NL tissue and LC tissue may contribute significantly to variations in the quantitative and qualitative profiles of PG synthesized in these tissues. Examples of the variability of PG production in triplicate samples of biopsy fragments of tissues (NL...
and LC) from three patients are summarized in Table 3. The mean coefficients of variation of PG measurements in biopsy fragments of NL and LC tissues obtained in triplicate from individual patients ranged from 7 to 32% for the 5 PG evaluated. The range of the intersample coefficients of variation in the measurements are approximately twice those reported earlier for intrasample replicate analysis (50). These findings indicate variations in cellular heterogeneity of NL as well as LC biopsy fragments used in these studies are not extreme and are within the expected range for human subjects.

PG Biosynthesis in NL Tissue

The profiles of production of 5 different eicosanoids from endogenous arachidonic acid in NL tissue fragments from 27 smokers and 15 current nonsmokers are shown in Fig. 1A. Appreciable mean levels of all 5 PG metabolites were present in NL tissue from both smokers and current nonsmokers. Low mean levels (<2 pmol/mg protein/15 min) were noted for PGE2 and PGF2α production in NL; intermediate levels (2–7 pmol/mg protein/15 min) were noted for PGD2 and 6-kPGF1α biosynthesis; and highest levels (>7 pmol/mg protein/15 min) were observed for TXB2. No significant differences were noted for levels of production of the PGs in NL tissue obtained from smokers and current nonsmokers or when PG biosynthesis was compared in NL tissue obtained from male and female patients (P > 0.30 in all instances; nonpaired, two-tailed Student's t test).

PG Biosynthesis in Human LC Tissue

The profiles of endogenous PG biosynthesis in unstimulated LC tissue from 27 smokers and 15 current nonsmokers are shown in Fig. 1B. High PG biosynthesis (>7 pmol/mg protein/15 min) was demonstrated for PGE2, PGF2α, and 6-kPGF1α as well as TXB2 in LC tissue. Conversely low mean levels of PGD2 (<2 pmol/mg protein/15 min) were observed consistently in lung tumor specimens. In addition, higher PGE2, 6-kPGF1α, and TXB2 mean levels were apparent in LC tissue obtained from cigarette smokers compared with those from current nonsmokers (P < 0.05 in all instances) and similar PGD2 and PGF2α levels were observed for LC tissue regardless of smoking status (P > 0.10 in all instances). Additionally, no significant differences in PG biosynthesis were observed in LC tissue obtained from male and female patients (P > 0.30).

Comparison of PG Biosynthesis in NL and LC Tissue

The profiles of PG biosynthesis from endogenous arachidonic acid in matched NL and LC tissue from individual patients are shown in Fig. 1. Elevated levels of PGE2 and PGF2α production were demonstrated in LC tissue compared to NL specimens irrespective of the patient’s smoking status (P < 0.05 in all instances; paired, two-tailed Student's t test). Higher levels of 6-kPGF1α were synthesized in LC tissues from individual smokers compared to those in NL tissue (P < 0.05). TXB2 levels were similar in lung tumor and normal pulmonary tissue from smokers (P > 0.05 in all instances), but lower TXB2 production was observed in LC than in NL tissue from current nonsmokers (P < 0.05). In contrast, levels of PGD2 production were higher in NL tissue fragments than in LC tissue regardless of the cigarette smoking status (P < 0.05 in all instances).

Table 1 Lung cancer patient population

<table>
<thead>
<tr>
<th>No.</th>
<th>Total</th>
<th>Male (mean age ± SD)</th>
<th>Female (mean age ± SD)</th>
</tr>
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<tr>
<td>42</td>
<td>23</td>
<td>(60 ± 11)</td>
<td>(59 ± 10)</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>(58 ± 30)</td>
<td>(45 ± 33)</td>
</tr>
</tbody>
</table>

Current nonsmokers are defined as those patients who have not actively smoked tobacco products for >6 months or who have never smoked. Only 1 patient with primary lung cancer and 1 patient with a metastatic lung tumor had no previous active smoking history. Mean time since cessation of smoking for former smokers was 4.5 years (range, 0.5–20 years).

Table 2 Histological classification of human lung tumors

<table>
<thead>
<tr>
<th>Cell type*</th>
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<tr>
<td>Primary</td>
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<tr>
<td>Squamous cell</td>
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<tr>
<td>Adenocarcinoma</td>
<td>7</td>
</tr>
<tr>
<td>Small cell</td>
<td>4</td>
</tr>
<tr>
<td>Large cell</td>
<td>3</td>
</tr>
<tr>
<td>Mixed tumors</td>
<td>2</td>
</tr>
<tr>
<td>Bronchioloalveolar cell</td>
<td>2</td>
</tr>
<tr>
<td>Bronchial carcinoid</td>
<td>1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>39</td>
</tr>
<tr>
<td>Metastatic</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma (prostate)</td>
<td>2</td>
</tr>
<tr>
<td>Transitional carcinoma (urinary bladder)</td>
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</tr>
<tr>
<td>Subtotal</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
</tr>
</tbody>
</table>

* All diagnoses were histologically confirmed.
* Primary pulmonary tumors.
* Numbers in parentheses, percentage.
* Tumors metastatic to the lung from a nonpulmonary source.

Table 3 Variability in prostanoid biosynthesis in different biopsy fragments of normal lung and lung carcinoma tissue from three patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Statistical analysis</th>
<th>Lung tumor fragments*</th>
<th>Normal lung fragments*</th>
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<tbody>
<tr>
<td>A</td>
<td>Mean</td>
<td>PGE2</td>
<td>PGD2</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0</td>
<td>0</td>
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<td>1.6</td>
</tr>
<tr>
<td></td>
<td>CV</td>
<td>30</td>
<td>28</td>
</tr>
</tbody>
</table>

* Patients diagnosed with adenocarcinoma (A) and squamous cell carcinomas (B and C).
* Endogenous prostanoid biosynthesis was performed on 0.5–1.0-mm3 normal lung and lung tumor tissue fragments as described in "Materials and Methods."
* n = 3.
* ND, not detectable; for purposes of statistical analyses, ND values were assumed to be 0.
* pmol/mg protein/15 min.
* CV, coefficient of variation = SD/mean × 100.
current nonsmokers and cigarette smokers with LC. A, comparison of PGE2, endogenous arachidonic acid precursor in unstimulated NL and LC tissue. Nonsmokers are defined as those patients who have not smoked tobacco products in any form, regardless of smoking status; and decreased TXB2 levels were observed for bronchial carcinoid tumors of the lung, large cell undifferentiated carcinomas of the lung, and metastatic tumors demonstrated similar levels of PGF2α production in NL and LC tissues (P > 0.05 in all instances). PGF2α production was higher in all other LCs studied than in the corresponding NL tissue from the individual patients (P > 0.05 in all instances; Fig. 3). In addition, the highest PGF2α production occurred in lung adenocarcinoma tissue.

PGD2. Profiles of endogenous PGD2 biosynthesis in unstimulated NL and LC tissue from individual LC patients according to histological cell type are demonstrated in Fig. 4. Similar levels of PGD2 production occurred in NL and LC tissue (P > 0.10 in all instances) with the exception of bronchioloalveolar cell carcinomas and large cell undifferentiated carcinomas where greater PGD2 production occurred in NL than in LC tissue (P < 0.05). In addition, elevated PGD2 production was evident in one bronchial carcinoid tumor in comparison with NL tissue (P < 0.05) (Fig. 4).

TXB2 and 6KPGF1α. Higher levels of TXB2 and lower levels of 6KPGF1α biosynthesis were observed for a bronchial carcinoid tumor removed from a patient compared with levels in NL tissue (Figs. 5 and 6; P < 0.05 in both instances). No other identifiable differences were noted between NL and LC tissue for TXB2 and 6KPGF1α production when these were evaluated in individual patients according to LC histological cell type (P > 0.10 in all cases).

When primary and metastatic lung tumors were compared, higher levels of all 5 PGs were consistently observed in primary compared to metastatic adenocarcinomas of the lung (Figs. 2–6; P < 0.05 in all instances).

**DISCUSSION**

Many biochemical pathways may be altered in human malignant disease (for review, see Refs. 51 and 52). Previous studies have suggested that there may be characteristic perturbations in PG biosynthesis in certain human lung carcinomas in vivo (13) and in lung carcinoma tissues in vitro (14). More recently, it has been demonstrated that characteristic profiles of PG biosynthesis occur in certain established human lung carcinoma cell lines (15–17). Since PGs may be important as mediators of normal pulmonary function as well as in the modulation of certain components of the immune response (38–43), tumor promotion (27–37), cellular proliferation (29–37), and tumor cell metastasis (24–26, 49), comparisons of the PG biosynthetic profiles in NL and LC tissues may provide additional insight into the role of this family of compounds in the pathophysiology of human LC. A major limitation in the assay methods for assessment of PG biosynthesis in earlier studies of LC patients (13) and in LC tissue in vitro (14) has been the requirement for large quantities of biological material. The recent development of highly sensitive mass spectrometric assays (50) permits rapid

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**Relationship between LC Histological Cell Type and PG Biosynthesis**

In order to further assess eicosanoid production from endogenous arachidonic acid precursor in unstimulated NL and LC tissue, patients were categorized according to tumor cell histological cell type and were then separately evaluated for production of each of the 5 PGs (Figs. 2–6).

**PGE2.** Profiles of endogenous PGE2 production in unstimulated NL tissue and LC tissue from individual LC patients according to histological cell type are shown in Fig. 2. The highest PGE2 production was observed in patients with squamous cell carcinomas or adenocarcinomas of the lung. Primary lung carcinomas demonstrated significantly higher PGE2 production than did metastatic tumors (P < 0.05 in all instances; nonpaired, two-tailed Student's t test). PGE2 production was consistently higher in tumor tissue for all histological cell types of primary lung carcinomas studied (P < 0.05 in all instances; paired, two-tailed Student's t test) with the exception of large cell undifferentiated carcinomas, where higher levels of PGE2 production were observed in NL tissue (P < 0.05) (Fig. 2).

**PGF2α.** Profiles of endogenous PGF2α production in unstimulated NL tissue and LC tissue from individual LC patients according to histological cell type are shown in Fig. 2. Similar levels of PGF2α production occurred in NL and LC tissue (P > 0.10 in all instances) with the exception of bronchioloalveolar cell carcinomas and large cell undifferentiated carcinomas where greater PGF2α production occurred in NL than in LC tissue (P < 0.05). In addition, elevated PGF2α production was evident in one bronchial carcinoid tumor in comparison with NL tissue (P < 0.05) (Fig. 4).

**TXB2 and 6KPGF1α.** Higher levels of TXB2 and lower levels of 6KPGF1α biosynthesis were observed for a bronchial carcinoid tumor removed from a patient compared with levels in NL tissue (Figs. 5 and 6; P < 0.05 in both instances). No other identifiable differences were noted between NL and LC tissue for TXB2 and 6KPGF1α production when these were evaluated in individual patients according to LC histological cell type (P > 0.10 in all cases).

When primary and metastatic lung tumors were compared, higher levels of all 5 PGs were consistently observed in primary compared to metastatic adenocarcinomas of the lung (Figs. 2–6; P < 0.05 in all instances).
PROSTANOID BIOSYNTHESIS IN HUMAN LUNG CANCERS

Fig. 2. Profiles of endogenous PGE2 production in matched unstimulated NL and carcinoma (CA) tissue according to tumor histological cell type. PGE2 levels were higher in all primary lung tumor histological cell types (P < 0.05 in all instances; paired, two-tailed Student's t test) with the exception of large cell undifferentiated carcinomas where PGE2 levels were higher in NL than in LC tissue (P < 0.05). No differences were noted in PGE2 production between metastatic tumors and NL tissue from individual patients (P > 0.03). Columns, mean; bars, SE. All data were derived from 15-min incubations.

Fig. 3. Profiles of endogenous PGF2α production in matched unstimulated NL and carcinoma (CA) tissue according to histological cell type. Higher PGF2α levels were noted in LC than NL tissue for squamous cell carcinomas, adenocarcinomas, mixed cell tumors, and a bronchiolar carcinoid (P < 0.05 in all instances). Columns, mean; bars, SE. All data were derived from 15-min incubations.

determinations of the biosynthetic profiles of PG in small (0.5–1.0 mm³) biopsy fragments of NL and LC tissues. The reproducibility of the assays (coefficients of intrasample variation < 15%) has also facilitated the current investigations of PG biosynthesis in NL and LC tissue fragments. Moderate variations [7–32% (Table 3)] in PG production were observed in separate NL and LC tissue fragments from individual patients or approximately twice the range in intrasample variation observed.
PROSTANOID BIOSYNTHESIS IN HUMAN LUNG CANCERS

Fig. 4. Profiles of endogenous PGD₂ production in matched unstimulated NL and carcinoma (CA) tissue according to histological cell type. Higher PGD₂ production was noted in NL than in LC tissue for bronchioalveolar cell carcinomas and large cell undifferentiated carcinomas ($P < 0.05$ in both instances) and in LC than NL tissue for one bronchial carcinoid ($P < 0.05$). All other comparisons were not significantly different. Columns, mean; bars, SE. All data were derived from 15-min incubations.

Fig. 5. Profiles of endogenous 6kPGF₁α production in matched unstimulated NL and LC tissues according to histological cell type. 6kPGF₁α levels were higher in NL from a patient than in a bronchial carcinoid tumor ($P < 0.05$). Otherwise, no differences were noted between carcinoma (CA) and NL tissue for the various histological cell types ($P > 0.05$ in all instances). Columns, mean; bars, SE. All data were derived from 15-min incubations.

for the current assay methods (50).

The relative contribution of tumor cells to the biosynthetic profiles of PGs in LC tissue is difficult to assess. An experimental design with tissue fragments cannot definitely distinguish the relative contribution of tumor cells to the total PG profiles from that of surrounding normal immune, stromal, hematopoietic, and/or parenchymal cells that may be present within tumor tissue fragments. The observed differences in the biosynthetic profiles of PG in matched NL and LC tissue from individual LC patients do, however, strongly suggest that these discrepancies may be related in part to selective PG biosynthesis in lung tumor cells. Recent investigations of PG biosynthesis in established cell lines derived from human lung carcinomas (15-17) which retain in vivo tumorigenicity in immunodeficient animals (53) have clearly demonstrated enhanced PGE₂, PGF₂α, and/or TXB₂ biosynthetic capabilities which further support the postulate that human tumor cells may contribute significantly to the profiles of PG biosynthesis in LC tissue.

In addition to the contribution of different cell populations to the PG biosynthetic profiles, the heterogeneity of the LC cells and the relative contribution of PG production in various LC subtypes must also be considered. Tumor cell heterogeneity...
Fig. 6. Profiles of endogenous TXB₂ biosynthesis in matched NL and LC tissue according to histological cell type. TXB₂ levels were higher in a bronchial carcinoid tumor than in NL tissue from the same patient (P < 0.05). No other differences were noted between NL and carcinoma (CA) tissue from individual patients (P > 0.10 in all instances). Columns, mean; bars, SE. All data were derived from 15-min incubations.

is specifically addressed when the PG profiles are evaluated according to LC histological classification. Enhanced PGE₂ and PGF₂α production was a characteristic feature of the majority of LC histological cell types in the present study with the highest levels of these two PGs being isolated from adenocarcinomas and squamous cell carcinomas of the lung. It is well established that considerable variation in histological type is often observed in individual lung tumor specimens and squamous cell carcinomas of the lung. It is well established human lung tumor cell lines. These studies have even more relevant in view of recently published studies in effect on the levels of PGE₂ and PGF₂α biosynthesis since the relative distribution of specific tumor cell subtypes (i.e., adenosquamous cell carcinomas and squamous cell carcinomas) within a given tumor. In contrast, the relative contribution of the large cell undifferentiated tumor cell population could have the opposite effect on the levels of PGE₂ and PGF₂α biosynthesis since the formation of these compounds in this tumor type is either similar to that observed in NL tissue or decreased. The potential importance of LC histological cell types to the relative contribution of the biosynthesis of different PG metabolites appears even more relevant in view of recently published studies in established human lung tumor cell lines. These studies have demonstrated considerable variation in PG biosynthesis in different cell lines representing different lung tumor histological cell types (15–17). Thus, there is a substantial independent body of evidence suggesting that certain tumor cell types present in human lung tumors may contribute directly to the currently observed profiles of PG biosynthesis in fresh LC tissue.

The current data provide documentation of the profiles of 5 PGs synthesized endogenously in individual NL tissue fragments via the fatty acid cyclooxygenase pathways. High levels of PGD₂, 6KPGF₁α, and TXB₂ and low levels of PGE₂ and PGF₂α production were shown in the normal pulmonary tissue fragments studied. These data confirm and extend previous reports which have measured the biosynthesis of individual PG in a given tissue specimen and have demonstrated low but detectable PGE₂ levels (10–12) as well as production of PGD₂ and TXB₂ (10–12, 50) in NL tissue.

The present studies also clearly demonstrate that the profiles of PG biosynthesis are altered in many human lung tumors and provide the first matched comparison of PG biosynthetic profiles in NL and LC tissue from individual LC patients. These results corroborate and extend previous investigations which have reported elevated PGE₂ production in vivo in certain human lung tumors, predominantly in primary squamous cell carcinomas of the lung (13–15). The present studies confirm that squamous cell carcinomas may have enhanced potential for the production of PGE₂ but also demonstrate that all human LC histological cell types (with the exception of large cell undifferentiated carcinoma of the lung) have enhanced PGE₂ production when compared with NL tissue from individual LC patients. Also of interest is the observation that tumors metastatic to the lung demonstrate levels of PGE₂ production similar to that of NL tissue, suggesting an organ specific relationship between PGE₂ production and tumor origin. Because PGE₂ has been postulated to be involved in certain aspects of immunoregulation (38–43), tumor promotion (27–37), pulmonary blood flow (10–12), and determination of tumor metastatic potential (24–26, 49), elevated PGE₂ levels might provide a selective advantage for tumor cell survival in the microenvironment of the lung. Further in vivo studies, with the use of the recently developed orthotopic animal model for the propagation of human lung tumors (53), may provide a suitable animal model for further investigations of the role of PGE₂ in LC pathobiology.

While PGE₂ production has been investigated previously in human LC, the biosynthesis of other cyclooxygenase products has not, heretofore, been studied in this disease. The present investigations offer the first documentation of PGF₂α, PGD₂, 6KPGF₁α, and TXB₂ production in individual human LC tissue fragments. The present report also provides the first direct comparison of production of these 5 PGs in NL and LC tissue from individual LC patients. PGF₂α production was greatly enhanced in pulmonary carcinoma tissue, but the mechanisms for enhanced PGF₂α biosynthesis in tumor tissue are not currently known. When PGF₂α production was analyzed according to histological cell type, squamous cell carcinomas, adenocarcinomas, bronchioloalveolar carcinomas, mixed cell carcinomas, and a bronchial carcinoid demonstrated enhanced PGF₂α production. Increased PGF₂α biosynthesis may result from stereospecific reduction of PGE₂ or could reflect other alterations in PG biosynthetic pathways in lung tumor tissue. The capability of LC to synthesize PGF₂α may be an important aspect of
tumor invasiveness and metastatic potential. PGF\textsubscript{2\alpha} has recently been shown to enhance type IV collagenase production in tumor cells in vitro, which, in turn, increases their ability to invade through basement membrane matrices (55).

The present studies also demonstrate that profiles of PGD\textsubscript{2}, 6KPGF\textsubscript{1\alpha}, and TXB\textsubscript{2} biosynthesis are altered in certain LC tissues from selected patients. The biochemical mechanisms for alteration of these specific PGs in selected human lung tumors are not presently known, but in the case of 6KPGF\textsubscript{1\alpha} or TXB\textsubscript{2} production, these could be related to the effects of cigarette smoking on tumor cell metabolic pathways. The elevation in TXB\textsubscript{2} biosynthesis could also result directly from enhanced TXB\textsubscript{2} production in tumor cells. Alternatively, enhanced platelet PG biosynthesis and/or increased platelet concentrations in LC tissues from smokers could partially account for the observed increase in TXB\textsubscript{2} levels. Recent reports by Hubbard et al. (16, 17) have demonstrated TXB\textsubscript{2} production in vitro in certain cell lines derived from human lung carcinomas supporting the concept that TX biosynthesis may occur in selected human lung tumor cells and that TXB\textsubscript{2} biosynthesis in LC cells could be important in the metastatic process.

The effect of active cigarette smoking on biosynthesis of PG is not currently understood. It is interesting that detectable differences in PG biosynthesis in LC tissue were observed between active smokers and patients who were not smoking at the time of study, even though the former pack/year history of smoking for the current nonsmokers was similar to that of the actively smoking patient group (Table 1). Certain metabolic pathways are enhanced by cigarette smoking (see Refs. 56 and 57 for review) and PG biosynthesis might also be enhanced as reflected by increased production of PGE\textsubscript{2}, 6KPGF\textsubscript{1\alpha}, and TXB\textsubscript{2} in LC tissue from smokers. It is well known that cigarette smoking induces specific cytochrome P-450 enzymes in human lung tissues (see Ref. 56 for a review) and previous studies have demonstrated alterations in certain cytochrome P-450 associated enzyme activities in patients with LC (58–62). Enhanced PG metabolism (via induction of cytochrome P-450 systems or via induction or repression of other enzymes involved in biosynthesis of these compounds) might, therefore, explain the elevated levels of selected PGs observed in LC tissue from smokers. Additional investigations, using relatively homogeneous human lung tumor cell lines, will, however, be required to delineate the specific enzyme(s) involved in this enhanced PG biosynthesis in human LC tissues. The effects of cigarette smoking on PG biosynthesis in LC might also have a significant secondary impact on tumor growth and metastatic potential, especially when PGE\textsubscript{2} and TXB\textsubscript{2} levels are affected (see previous discussion).

It is apparent from the present studies that the use of an individual LC patient’s tumor and NL tissue provides a novel method for biochemically profiling PG biosynthesis in small tissue fragments and in some cases for initial characterization of LC biochemically. This appears to be notable for both primary large cell undifferentiated carcinomas of the lung and adenocarcinomas metastatic to the lung, although the number of tumors studied in each group was small (N = 3). Large cell undifferentiated carcinoma of the lung which, heretofore, was thought to be an undifferentiated carcinoma devoid of any characteristic biochemical features (6, 7) demonstrated specific alterations in PGD\textsubscript{2} and PGE\textsubscript{2} biosynthesis which appeared to be characteristic of only this LC cell type. Adenocarcinomas metastatic to the lung also demonstrated lower levels of all 5 PGs studied compared to primary adenocarcinomas of the lung and these specific alterations in PG metabolic profiles could prove to be useful in distinguishing these particular lung tumors from other LC cell types. It should be emphasized that further studies, involving large numbers of primary large cell undifferentiated LC and adenocarcinomas metastatic to the lung, will be required to confirm these preliminary observations. Moreover, detailed studies of endogenous PG biosynthesis in established human LC cell lines derived from fresh tumor material may provide better characterization of the specific metabolic pathways involved and allow further investigation of the role of altered PG patterns in the pathogenesis of human LC.

In summary, the present studies demonstrate that biosynthetic profiles of bisenoic PG and TXB\textsubscript{2} differ in matched NL and LC tissues from individual LC patients. The discrepancies in the biosynthetic profiles of the two tissues may result, in part, from altered PG biosynthesis in lung tumor cells. Further investigations of PG biosynthesis in human LC are required, however, for a more complete understanding of the role of this family of compounds in LC as well as normal pulmonary tissue biology.

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