Advances in Brief

**Immunohistochemical Expression of Cyclooxygenase Isoenzymes and Downstream Enzymes in Human Lung Tumors**

Leander Ermert,\(^1\) Christian Dierkes, and Monika Ermert

Department of Pathology, Justus-Liebig-University Giessen, 35385 Giessen, Germany

**Abstract**

**Purpose:** Prostanoids are important mediators of pulmonary vaso- and bronchotone regulation and strongly influence inflammatory reactivity. The product of cyclooxygenase (Cox), prostaglandin H\(_2\), is further metabolized via downstream enzymes into the different effective metabolites. The specific cellular equipment with certain downstream enzymes crucially determines the cellular reaction by generation of functionally different prostanoid metabolites.

**Experimental Design:** To elucidate the role of arachidonic acid metabolism via the cyclooxygenase pathway in different human lung tumors, expression of cyclooxygenase isoenzymes (Cox-1 and Cox-2) and downstream enzymes of prostanoid metabolism was investigated in human non-small cell lung cancer and normal human lung tissue by immunohistochemical techniques.

**Results:** In comparison to strong Cox-1 reactivity in airways and endothelial cells of normal lung specimens, only 4 of 15 adenocarcinomas showed infrequent Cox-1 expression. All lung cancer specimens displayed an increased Cox-2 immunostaining pattern with strong reactivity in adenocarcinomas and lower reactivity in squamous cell carcinomas. Adenocarcinomas and squamous cell carcinomas were also positive for thromboxane A\(_2\) synthase, prostaglandin D\(_2\) synthase, and prostaglandin E\(_2\) synthase, but not for prostacyclin synthase. Endothelial cells of vessels found within or near the tumor showed extensive immunostaining of Cox-2 and thromboxane A\(_2\) synthase, whereas endothelial cells of normal lung specimens, in contrast, expressed Cox-1 and prostacyclin synthase.

**Conclusions:** We conclude that non-small cell lung cancer shows a specific Cox-2-specific expression pattern, which is specifically altered in lung tumor cells and tumor supplying vessels in contrast to normal lung tissue. This may have major impact on tumor progression and tumor-associated inflammation via an altered prostanoid metabolism with consecutive tumor-associated blood flow distribution.

**Introduction**

Lung cancer is by far the leading cause of cancer-related deaths. From recent studies in animal models, strong evidence points to prostanoids playing a key role in tumor progression via their influence on angiogenesis, tumor growth, and metastatic settlement (1–3). The rate-limiting enzymes for prostaglandin and thromboxane production derived from arachidonic acid (AA)\(^2\) are the cyclooxygenase (Cox) isoenzymes Cox-1 and Cox-2. Both cyclooxygenases are constitutively expressed in most tissues, but Cox-2, in contrast to Cox-1, is the mitogen-inducible isoform. In lipopolysaccharide (LPS)-treated lung tissue Cox-2 has been shown to be up-regulated in different pulmonary cell types with major impact on LPS-induced vaso- and bronchotone regulation (4). Several studies have provided evidence that Cox-2 is induced in human tumors by cytokines, endotoxins, and tumor promoters (5–8). Different types of cancer, such as human colonic (9), pancreatic (10, 11), skin (12) and lung cancer (13), express high levels of Cox-2. Epidemiological studies have demonstrated a 50% reduction in the rate of mortality from colorectal cancer in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs; see Ref. 14), which are selective inhibitors of both cyclooxygenase isoenzymes. However, selective inhibition of Cox-2 seemed to be more effective in antiinflammatory and antitumor therapy (8, 15). Disruption of the gene encoding Cox-2 in APC\(^{−/−}\) mice, a model of familial adenomatous polyposis, markedly reduced size and number of intestinal polyps (16, 17). Increased expression of Cox-2 has been detected in different types of lung cancer, particularly in adenocarcinomas, and has been considered to be characteristic for an invasive and metastatic phenotype (18). Moreover, Celecoxib, a selective Cox-2-inhibitor, dose-dependently inhibited tumor growth and the number and size of lung metastases in Lewis lung carcinoma (8). Taken together, these data provide strong evidence for the importance of Cox-2 enzyme activity in lung cancer oncogenesis.

In recent studies, evidence has been emerging that tumour-promoting effects of Cox-2-overexpression may be attributable to specific products of further AA metabolism (19). Downstream enzymes of Cox-isoenzymes generate different metabolites of AA with partially antagonistic effects on target cells. TXA\(_2\), e.g., is a potent vasoconstrictive agent, whereas PGI\(_2\) exerts dilative effects. TXA\(_2\) and PGE\(_2\) have been shown to be proinflammatory mediators, whereas PGI\(_2\) is an anti-inflammatory prostaglandin (20). In cultured tumor cell lines, the influ-

\(^1\)To whom requests for reprints should be addressed, at Institut für Pathologie, Langhansstr. 10, 35385 Giessen, Germany. Fax: 49-6441-212253; E-mail: leander.ermert@anatomic.med.uni-giessen.de.

\(^2\)The abbreviations used are: AA, arachidonic acid; Cox, cyclooxygenase; LPS, lipopolysaccharide; NSAID, nonsteroidal anti-inflammatory drug; NSCLC, non-small cell lung cancer; PGE-S, prostaglandin E\(_2\) synthase; PGD-S, prostaglandin D\(_2\) synthase; PGI-S, prostacyclin synthase; TXA-S, thromboxane A\(_2\) synthase.
Fig. 1 Human NSCLC; the left panel shows squamous cell carcinomas, the middle panel displays adenocarcinomas, each stained with different antibodies to Cox-1/Cox-2 or related downstream enzymes. Normal lung vasculature (I) and tumor-associated vessels within adenocarcinomas (J and L) and a squamous cell carcinoma (K) are shown on the right panel. Note, that Cox-1 is not expressed in squamous cell carcinoma (A), whereas Cox-2 is overexpressed (B). The downstream enzymes PGD-S (C) and PGE-S (D) are both found consistently expressed within squamous cell carcinomas. Adenocarcinomas were negative for PGI-S (E), but positive for TXA-S (F), PGD-S (G), and PGE-S (H) expression. Endothelial cells (EC) were found to express PGI-S throughout normal lung tissue (I). Endothelial cells of tumor-associated vessels showed new immunostaining for Cox-2 (J) and TXA-S (K) and low immunostaining for PGE-S (L). The scale bar (100 μm in I) refers to all images.
ence of TXA$_2$ and PGE$_2$ on tumor-associated angiogenesis was correlated with tumor-induced increase of TXA$_2$ and PGE$_2$ (19, 21). Although several studies have found an increased expression of Cox-2 in human lung tumor cells (22, 23), little is known about expression of Cox-1, as well as the downstream enzymes of Cox-dependent prostanoid metabolism. Previous studies investigating tumor cell lines of different human lung tumors postulated that the prostaglandin biosynthesis profile of malignant cells may differ from that of normal lung tissue (24, 25).

In the current study, the specific cellular expression patterns of the Cox-isoenzymes and downstream enzymes of prostanoid synthesis were immunohistochemically evaluated in different types of non-small cell lung cancer (NSCLC) in comparison with normal human lung tissue. Provided that tumors generate different profiles of prostanoid metabolites, specific tumor-related cellular enzyme expression patterns may underlie this observation. Such tumor-related metabolic pathways may have major impact on tumorigenesis and tumor-associated angiogenesis.

**Materials and Methods**

**Reagents.** The Cox-1 antibody (affinity purified goat polyclonal IgG) was obtained from Santa Cruz Biotechnology (Santa Cruz, CA). The Cox-1 antibody was prepared against a peptide corresponding to the amino acid sequence 583–602 mapping at the COOH-terminus of Cox-1. The anti-Cox-2 antibody is directed against amino acids 27–46 of the amino terminus of Cox-2 (affinity purified goat polyclonal IgG; Santa Cruz Biotechnology). Both antibodies bind specifically to one of the isoenzymes and do not cross-react. Antibodies against PGD-S (rabbit polyclonal IgG), and PGI-S (mouse monoclonal IgG) were obtained from Oxford Bio-medical Research Inc. (Oxford, MI). The antibody against PGE-S (affinity purified rabbit polyclonal IgG) was obtained from Cayman Chemical (Ann Arbor, MI). The PGE-S antibody was prepared against a peptide corresponding to the amino acid sequence 59–75. The anti-TXA$_2$-antibody (directed against the purified enzyme from porcine lung) and the secondary antibodies were developed with a Vector Red Substrate Kit (Camon, Wiesbaden, Germany). Levamisol (2.5 mM) was added to inhibit endogenous alkaline phosphatase activity.

Counterstaining of the sections was performed with Mayer’s hematoxylin. Control staining was performed by omission of the primary antibody and substitution with nonspecific serum at the same dilution.

**Evaluation of Immunostaining Intensity.** Evaluation of the immunohistochemical staining was performed by at least two independent observers applying a semiquantitative score according to recently published studies (26). The immunostained samples were scored to display absent (0), weak (+), moderate (++), or strong (+++) staining intensity. The analysis was blind, and the reproducibility of scoring was determined on a second occasion when the slides were reviewed by the same individuals in a blind fashion.

**Results**

Forty-eight cases of human lung tumors were evaluated for Cox-1 expression using immunohistochemistry. Only 4 of 15 adenocarcinomas and the chondrohamartomas showed a moderate immunostaining intensity for Cox-1. There was no expression of Cox-1 in squamous cell carcinomas (Fig. 1A) and in vascular smooth muscle cells or endothelial cells of pulmonary vessels located within the tumor or adjacent to the tumor (Table 1). In contrast, normal human lungs showed a moderate immunostaining of Cox-1 in bronchial epithelial cells and in endothelial cells of pulmonary vessels (Table 1).

The immunohistochemical expression patterns of Cox-1 and Cox-2 in normal human lung tissue corresponded well to the findings recently reported for nonstimulated rat lung tissue (27).

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**Table 1** Immunohistochemical expression of Cox-1 and Cox-2

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cox-1</th>
<th>Cox-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human lung cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0/++</td>
<td>++</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Tumor supplying vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular smooth muscle cells</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Normal lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial epithelial cells</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular smooth muscle cells</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>++</td>
<td>0</td>
</tr>
</tbody>
</table>

*The immunostained samples were scored to display absent (0), weak (+), moderate (++), or strong (+++) staining intensity.*
In agreement with these findings in rat lungs (27), we detected a low expression pattern of Cox-2 in bronchial epithelial cells and vascular smooth muscle cells in normal human lung tissue (Table 1). No expression of Cox-2 was found in endothelial cells of pulmonary vessels within normal lung specimens (Table 1). We detected a differential expression pattern for both Cox-isoenzymes concerning tumor types and tumor-associated vessels. In NSCLC, the strongest immunostaining for Cox-2 was found in epithelial cells of adenocarcinomas (Table 1). Epithelial cells of squamous cell carcinomas showed a moderate expression pattern of Cox-2 (Table 1 and Fig. 1B). In addition, Cox-2 immunostaining was found within endothelial cells of pulmonary vessels nearby or within the tumor, which was in contrast to normal lung tissue (Table 1 and Fig. 1J).

Among the downstream enzymes, we detected a moderate immunostaining intensity for PGE-S in epithelial cells of adenocarcinomas (Table 2 and Fig. 1H) and squamous cell carcinomas (Table 2 and Fig. 1D), which represents a decrease of staining intensity compared with the strong immunostaining for PGE-S seen in bronchial epithelial cells of normal lungs (Table 2). Interestingly, we found only low expression of PGE-S in endothelial cells of pulmonary vessels that were located within or nearby the different lung tumors (Table 2 and Fig. 1L). In contrast, endothelial cells of pulmonary vessels in normal lung tissue showed strong expression of PGE-S (Table 2). TXA-S was found to be moderately stained in bronchial epithelial cells and low in vascular smooth muscle cells in normal lung specimens (Table 2). There was no significant change in the level of immunostaining comparing epithelial cells of adenocarcinomas and bronchial epithelial cells of normal lung specimens (Table 2 and Fig. 1F).

Table 2 Immunohistochemical expression of downstream enzymes

<table>
<thead>
<tr>
<th>Groups</th>
<th>PGE-S</th>
<th>PGD-S</th>
<th>TXA-S</th>
<th>PGI-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human lung cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>++*</td>
<td>++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>+++</td>
<td>+++</td>
<td>+/0</td>
<td>0</td>
</tr>
<tr>
<td>Tumor-supplying vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular smooth muscle cells</td>
<td>0</td>
<td>0</td>
<td>+/0</td>
<td>0</td>
</tr>
<tr>
<td>Endothelial cells</td>
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<td>+++</td>
<td>+++</td>
<td>0</td>
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<td>Normal lung</td>
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<tr>
<td>Bronchial epithelial cells</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
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<tr>
<td>Pulmonary vessels</td>
<td></td>
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<tr>
<td>Vascular smooth muscle cells</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Endothelial cells</td>
<td>+++</td>
<td>+</td>
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<td>++</td>
</tr>
</tbody>
</table>

* The immunostained samples were scored to display absent (0), weak (+), moderate (++), or strong (+++) staining intensity.

A striking difference was detected concerning the staining intensity of PGI-S between tumor and normal lung specimens. Although vascular endothelial cells of normal lung specimens showed a moderate staining intensity for PGI-S (Table 2 and Fig. 1I), it was not possible to detect any expression of PGI-S in vascular endothelial cells of tumor-associated vessels (Table 2). In contrast to all other downstream enzymes, PGI-S was not detected in any of the different tumor specimens (Table 2).

The two chondrohamartomas that were investigated in this study showed expression patterns of downstream enzymes similar to those of normal lungs. Cox-2 expression was altered and showed a strong expression in bronchial epithelial cells associated with chondrohamartoma. Infiltrating leukocytes were found in most tumor specimens of both adenocarcinomas and squamous cell carcinomas and were positive for both Cox-isoenzymes and all of the downstream enzymes examined.

Discussion

Tumor-induced activity of Cox-2 and related downstream enzymes has been implicated to play a crucial role in enhanced tumor invasion and metastasis (28), angiogenesis (29, 30), decreased host immunity (1), and apoptosis resistance (29). To date, most of the studies have focused on the expression of Cox-2 and its possible role in oncogenesis and cancer growth (2, 3). Although both Cox-1 and Cox-2 have been shown to be constitutively expressed in many cell types in several organ systems (31, 32), Cox-2 is known to be the mitogen-inducible isoform (5–8). In rat lungs, a cell type-specific expression pattern for both isoenzymes was found under physiological conditions (27). Cox-1 was predominantly localized to bronchial epithelial cells, smooth muscle cells of large hilum veins, endothelial cells of pulmonary vessels, and alveolar macrophages, whereas Cox-2 staining was detected most intensively in peri-bronchial leukocytes, smooth muscle cells of partially muscular bronchial arteries, and bronchial epithelial cells of normal lung tissue (Table 2). In contrast, we found an increase in PGD-S staining intensity in vascular endothelial cells of tumor-associated vessels in comparison to pulmonary vessels of normal lung tissue (Table 2). No expression of PGD-S was found in vascular smooth muscle cells either in the tumor tissue or in normal lung specimens (Table 2).
bronchotone regulation via prostanoid formation under physiological conditions (33). Increased expression of Cox-2 resulting in enhanced response to secondary applied stimuli has been demonstrated in LPS-primed rat lungs (4, 34). Thus, the Cox-2 regulated AA metabolism plays a pivotal role under pathophysiological conditions, e.g., in endotoxin-induced inflammatory lung injury (4), which may also apply to the clinical situation of patients suffering from acute respiratory distress syndrome under conditions of sepsis.

In the current study, the cellular expression of both Cox isoenzymes and their downstream enzymes in NSCLC was investigated to clarify metabolic pathways of AA metabolism and their possible involvement in tumor growth and neovascularization. In comparison to normal lung specimens, we found a decrease in Cox-1 immunostaining in endothelial cells of tumor-associated pulmonary vessels, as well as in tumor cells of NSCLC. In contrast, Cox-2 immunostaining was markedly increased in most specimens of NSCLC, particularly in tumor cells and was additionally expressed in endothelial cells of tumor-associated vessels.

Cox-2 immunostaining within the tumor-induced vasculature and preexisting vasculature adjacent to cancer lesions in colonic, prostate, breast, and lung cancer supported the view that Cox-2 may play a major role in angiogenesis of tumor-supplying vessels (8), in contrast to overexpression of Cox-1 in ECV immortalized endothelial cells injected intradermally into nude mice (35). However, tumor growth could not be inhibited by indomethacin; thus, a nonprostanoid function of transfected Cox-1 expression was assumed to account for the observed tumorigenesis (35).

The current study, in accordance with recently published reports (8, 13, 18, 22), demonstrates increased expression of Cox-2 and simultaneous down-regulation of Cox-1 in NSCLC, particularly in adenocarcinomas. The tumor-associated up-regulation of Cox-2 expression may be regarded as a particular feature of tumorigenesis and development of an invasive type of NSCLC correlating with high levels of Cox-2 expression in lymph node metastases of human lung tumors (18).

An increased Cox-2 expression was observed in gastric carcinoma (36, 37) and carcinoma of the prostate (38), as well as in dermal carcinoma (12) and carcinoma of head and neck (39). Whereas Cox-2 overexpression was also correlated with invasion and metastasis in pancreatic adenocarcinoma and carcinoma of the cervix (10, 11, 40), adenocarcinoma of the ovary, in contrast, showed an overexpression of Cox-1 (41). However, a correlation between Cox-1 expression and the grade of malignancy of ovary carcinoma was not observed (41). An inhibitory effect of NSAIDs and selective Cox-2 inhibitors on tumorigenesis and tumor growth in colonic and pulmonary tumors has been shown in vivo and in vitro (2, 15). This effect may be related to the suppression of PGE2-mediated angiogenesis and production of vascular endothelial growth factor (8, 21, 42). In addition to several experimental studies, clinical studies evaluating the therapeutic benefit of Cox-2-selective inhibitors for anticancer therapy are now performed (43, 44).

The pivotal role of Cox-2 for tumor growth and development results from its key position within the AA metabolism. Downstream to the Cox enzymatic reaction, several alternative enzymes generate prostanoid metabolites with different, sometimes antagonistic, effects. Within the lung, prostanooids have major impact on broncho- and vascular tone regulation under physiological and pathological conditions (4, 33, 34). TXA2 and PGD2 are very potent vaso- and bronchoconstrictive agents in contrast to the vasodilator platelet-activating factor (PAF) (50). Concerning tumor-related effects, the metabolite PGE2, in particular, has been examined in recent studies and was assumed to play a role for tumor-associated neovascularization and tumor growth (21, 24, 25, 45). Because PGE2 seems to stimulate neovascularization via PGE2-mediated tube formation and vascular endothelial growth factor production (46), PGE2 might be a possible target for pharmacological anticancer therapy.

In the present study, we have demonstrated cellular-expression patterns for prostanoid and thromboxane synthases in different NSCLCs. PGE-S expression was detected in tumor cells of both human lung adenocarcinomas and squamous cell carcinomas. Interestingly, endothelial cells of tumor-associated pulmonary vessels displayed only low PGE-S expression in contrast to high levels of staining intensity observed in endothelial cells of pulmonary vessels in normal lung specimens. Thus, growth of tumor-induced neovascularization may be stimulated by PGE2 release from the tumor cells.

PGE2 was recently discussed with regard to triggering a positive feedback loop in colon-cancer tissues via the EP2 receptor (17). In NS-398-treated HUVEC-cells, PGE2 has been shown to promote a vasoconstrictive activation of the small GTPases Cdc42 and Rac, resulting in induction of endothelial cell spreading and migration in vitro (47). In addition, there has been increasing evidence that PGE2 might influence host immune regulation via suppression of T-cell stimulation and natural killer cell activity (1, 48, 49). Moreover, tumor-released PGE2 may influence considerably the distribution of intrapulmonary blood flow and may thus enhance blood supply and tumor growth.

In contrast, only a few studies have examined the generation of other prostanoids, such as TXA2, PGL2, or PGD2, or the expression of related prostanoids in lung cancer tissue (24, 25). In freshly obtained normal and lung cancer tissue, prostaglandin biosynthesis was evaluated by measuring mean levels of different prostaglandin metabolites within tissue homogenates (24, 25, 50). However, no significant differences concerning the prostaglandin biosynthesis of TXA2, PGL2, and PGD2 between normal tissue and cancer tissue could be obtained in these studies (25).

In the current study, we detected an increased level of staining intensity for PGD-S in endothelial cells of tumor-associated pulmonary vessels that may be connected with tumor-related angiogenesis and neovascularization. Moreover, PGD-S was found to be expressed in adenocarcinomas and squamous cell carcinomas. PGD2 has been shown in several studies to cause a vasoconstriction within the pulmonary vasculature (20). Thus, increased release of PGD2 into the tumor-surrounding vasculature may substantially influence local blood flow. On the other hand, it has been assumed that PGD2 may inhibit tumor growth and prolong survival time of nude mice bearing human ovarian carcinoma (51). However, the increase in immunohistochemical expression of PGD-S in endothelial cells of NSCLC-associated vessels supports a tumor-promoting function of PGD2 generation in lung tumor cells and tumor-supplying vessels.

TXA2 is known to be a strong activator of platelet aggregation (52), contraction of vascular smooth muscle cells (53), and release of prostacyclin (PGL2) from endothelial cells (54). Moreover, platelets, which constitutively contain TXA-S, have...
been shown to be important for tumor angiogenesis (19, 55). In the current study, we detected TXA-S expression in adenocarcinomas comparable with normal bronchial epithelial cells, whereas TXA-S expression in squamous cell carcinomas was suppressed. In addition, we found positive immunostaining for TXA-S in endothelial cells of tumor-associated pulmonary vessels in contrast to endothelial cells within normal lung tissue, which did not express TXA-S. These findings support the view that TXA-S may promote angiogenesis, as was recently suggested by cell culture studies showing endothelial cell migration stimulated by a TXA-S mimetic (19). Moreover, high levels of TxB2, the stable metabolite of TXA-S, have been detected in matched tissues of human lung cancer (25). Because TXA-S is known to stimulate PGI2 release in endothelial cells, it might be a surprising finding that no significant levels of PGI-S were detectable in lung tumor cells in our studies. Even the constitutive expression of PGI-S detected in endothelial cells within normal lung tissue was suppressed within the tumor-associated vasculature. In a recent study, the stable metabolites of TXA-S and PGI2 were evaluated by ELISA in colon cancer and breast cancer tissue homogenates (56). In accordance with our results, low levels of PGI2 metabolites were measured in contrast to increased TXA-S levels, particularly in colon cancer tissue (56).

In addition to a possible growth-inducing capacity during angiogenesis (3, 8, 29), an important feature of all prostanoids metabolites within the lung vasculature is their effect on vasmotor activity, thus influencing vascular pressure and local pulmonary blood flow. In the current study, an interesting switch concerning enzyme expression of Cox-isoenzymes and related downstream enzymes was observed in endothelial cells of tumor-associated vessels. In contrast to normal lung vessels, endothelial cells of tumor-associated vessels expressed Cox-2 instead of Cox-1 and TXA-S instead of PGI-S. In addition, PGD-S expression was enhanced, whereas PGE-S expression was decreased in endothelial cells of tumor-associated vessels in contrast to normal vascular endothelial cells. The metabolites TxA2 and PGD2 in particular, have been shown to cause vasoconstriction within the pulmonary vasculature, whereas PGI2, in contrast, exerts strong vasodilative effects (20). Thus, enhanced generation of vasoconstrictive mediators may induce local vasoconstriction within the tumor-surrounding pulmonary parenchyma and may lead to increased blood supply improving tumor growth and cancer cell survival.

In conclusion, our results implicate an important role for Cox-2 and related prostanoid-synthases-dependent AA metabolism in tumor-induced angiogenesis and neovascularization in human lung tumors. In addition, tumor-induced alteration of the balance between vasoconstrictive and vasodilative mediator generation promotes redistribution of lung blood flow to optimize tumor blood supply.

Further investigation is therefore warranted to determine the putative roles of PGE-S and TXA-S in the development and progression of lung cancers. In addition, our results might implicate specific enzymes of prostanoid metabolism as potential targets of chemopreventive strategies aimed at NSCLC.

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References


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