Editorial

Prostaglandin E Synthase: Another Enzyme in the Cyclooxygenase Pathway Driving Epithelial Cancer?

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COX-2 in Epithelial Cancer

COX-1 and -2 metabolize AA and other 20-carbon polyunsaturated fatty acids into PGs, which have a wide array of biological roles that are tissue-specific (1). A variety of exogenous stimuli increase the expression of COX-2 but not COX-1 as a consequence of their distinct transcriptional and translational regulation. Although the enzymatic reaction they catalyze is the same, COX-1 and -2 exhibit different substrate specificities (2). With its distinct properties, it was not surprising that COX-2 was found to play a unique role in epithelial tumorigenesis.

A large body of genetic and biochemical evidence supports a role for COX-2 in human CRC. COX-2 expression and enzymatic activity are increased in colonic epithelial premalignancy and invasive disease (3). Treatment of CRC cells with PGE2 or PGJ2, which are COX-2-induced AA metabolites, induces cellular proliferation (4). Rat intestinal epithelial cells that overexpress COX-2 take on phenotypic changes that could enhance their tumorigenic potential (5). Conversely, carcinogen-induced CRC is reduced in mice that are COX-2-null and by cotreatment with COX-2 enzymatic inhibitors (6–8). Most interestingly, recently completed clinical trials demonstrated that chronic administration of a COX-2 inhibitor reduced the formation of adenomatous colonic polyps in patients at high risk (9).

Additional studies support a role for COX-2 in a variety of other epithelial cancers including lung cancer. NSCLCs and premalignant bronchial and alveolar lesions express increased levels of COX-2 (10, 11). COX-2 has pleiotropic effects on the bronchial epithelium that culminate in malignancy, including proangiogenesis, epithelial mitogenesis and antiapoptosis, and local immune suppression (Fig. 1; Refs. 5, 12, 13). Supporting a role for COX-2 in lung carcinogenesis, COX-2 inhibitors reduced lung tumor formation in carcinogen-treated animal models (14, 15). In addition to its direct effects on the bronchial epithelium, COX-2 may indirectly promote lung cancer by stimulating the formation of carcinogenic metabolites of cigarette smoke (16). In turn, components of tobacco smoke activate COX-2 and increase the conversion of phospholipids to AA, a COX-2 substrate (17, 18). Thus, cigarette consumption creates a feed-forward loop involving activation of COX-2 and tobacco smoke metabolism.

Prostaglandin E Synthase in NSCLC

Whereas the evidence supporting a role for COX-2 in epithelial cancer is strong, the mechanisms responsible for the carcinogenic effect of COX-2 have not been fully defined. COX enzymes catalyze the formation of PGH2, the unstable bicycloendotheloxyridine intermediate, which undergoes additional metabolism to the parent eicosanoids PGD2, PGE2, PGF2, and thromboxane A2 (Fig. 2). Of these, PGE2 is most clearly implicated in lung cancer. PGE2 levels are elevated in the bronchial fluid of NSCLC patients, and it induces local immune suppression, which may be important in malignant progression (12, 19, 20). A role for PGE2 is supported by data reported by Yoshimatsu et al. (21) who investigated the expression of PGES, a glutathione-dependent, membrane-bound enzyme that converts PGH2 into PGE2. Yoshimatsu et al. (21) demonstrated that PGES levels were increased in NSCLCs relative to normal tissue, and mutant ras, which is found in 30–50% of lung adenocarcinomas, activated PGES gene transcription. Interestingly, PGES and COX-2 were frequently coexpressed in tumor tissue.

In contrast to NSCLC cells, immortalized BEAS-2B human bronchial epithelial cells did not express PGES, providing evidence that PGES is expressed as a consequence of malignant transformation. Additional studies should be performed to identify whether PGES is expressed in premalignant lesions of the bronchus (metaplasia or dysplasia) or peripheral lung (atypical alveolar hyperplasia), which would have important implications for PGES as a target in lung cancer chemopreventive strategies. Additionally, cytokine treatment increased PGES levels only in NSCLC cells. This raises the possibility that fully transformed cells are unique in the ability to express a competence factor required for PGES expression. One candidate is p53, which induces PGES expression and is inactivated in BEAS-2B cells as a consequence of SV40 T-antigen expression (23, 24).

COX-2 and PGES are inducible enzymes that are components of the same pathway. Several tumors expressed COX-2 at much higher levels than PGES, which is consistent with genetic evidence from in vitro models in which COX-2 overexpression alone is sufficient to induce a transformed phenotype (5). However, Yoshimatsu et al. (21) found that COX-2 and PGES are frequently coexpressed in NSCLC tumors. Alterations of two molecules involved in a common pathway are not consistent with the expected pattern of genetic or biochemical alterations in human cancer, which usually involves alterations of a single pathway component. For example, the retinoblastoma pathway...
is blocked through either inactivation of a tumor suppressor (retinoblastoma or the p16 cyclin-dependent kinase inhibitor) or overexpression of an oncoprotein (cyclin D1 or cyclin depend-  
dent kinase-4; Ref. 25).

One possible explanation for this apparent inconsistency is that COX-2 and PGES act synergistically to drive PGE$_2$ production. This hypothesis is consistent with previous reports that COX-2 and PGES are coregulated, and PGE$_2$ biosynthesis may depend on the presence of both of these enzymes (22). If PGE$_2$ is an important mediator of COX-2 transformation, coexpression could be advantageous from the standpoint of clonal evolution. In this setting, COX-2 and PGES coexpression may be important from the standpoint of the natural history of the disease and response to treatment. Elucidating this will require prospective evaluation of NSCLC patients in clinical trials.

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**Fig. 1** A schematic diagram illustrating that cigarette smoke carcinogens activate COX-2 pathways, COX-2 induces formation of cigarette smoke carcinogenic metabolites, and COX-2 induces multiple biologic effects that may play a role in lung carcinogenesis. PL, phospholipids.

**Fig. 2** A schematic diagram illustrating that COX-2 activates the formation of PGH$_2$ from AA, which is converted into PGE$_2$ by PGES and multiple other PGs and thromboxane A$_2$. 
REFERENCES


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