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

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COX-2 in Epithelial Cancer

COX-12 and -2 metabolize AA and other 20-carbon poly-unsaturated 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 carcinogenic stimuli increase the expression of COX-2 but not COX-1 (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 evidence that PGES is expressed as a consequence of malignant transformation. Additional studies should be performed to identify how 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 levels 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) demonstrated 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

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2 The abbreviations used are: COX, cyclooxygenase; AA, arachidonic acid; PG, prostaglandin; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; PGES, prostaglandin E synthase.
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 dependent kinase-4; Ref. 25).

One possible explanation for this apparent inconsistency is that COX-2 and PGES act synergistically to drive PGE₂ production. This hypothesis is consistent with previous reports that COX-2 and PGES are coregulated, and PGE₂ biosynthesis may depend on the presence of both of these enzymes (22). If PGE₂ 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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