Deregulated inflammatory mediators and growth factors seem to act in concert with mutational events in driving malignant transformation and progression, thus contributing to the complex pulmonary environment in the lung at risk for cancer. Pulmonary diseases that are associated with the greatest risk for malignancy are characterized by abundant and deregulated inflammation (1). Profound abnormalities in inflammatory-fibrotic pathways evident in chronic obstructive pulmonary disease/emphysema, pulmonary fibrosis, and other pulmonary disorders continue in exaggerated fashion in the setting of established lung cancer (2). For example, the procarcinogenic prostaglandins (PG), which are released in these settings, contribute to the aberrant production of cytokines and growth factors. This finding led to the research focus on cyclooxygenase (COX; also referred to as PG endoperoxidase or PGG hydroperoxide synthase), the rate-limiting enzyme for the production of PGs and thromboxanes from free arachidonic acid released from membrane phospholipids by phospholipase A2 (3).

Two COX isoforms, COX-1 and COX-2, have been studied extensively. COX-1 is constitutively expressed in most cells and tissues. The inducible isoenzyme COX-2 is an immediate early response gene expressed following exposure to cytokines, growth factors, and other stimuli, thus enhancing eicosanoid production during inflammation. COXs are bifunctional enzymes, with fatty acid COX activity and PG hydrolase activity ultimately producing PGH2 (4). PGH2 is converted to a variety of eicosanoids by individual PG synthases that are often expressed in a cell type–dependent manner. The COX isoforms share the same structural features including a hydrophobic channel that allows arachidonic acid to access the COX catalytic site (5). Therefore, relative production of the various COX products depends on the cellular concentrations of COX enzymes as well as downstream metabolic and catabolic enzymes within the COX pathway.

Whereas the COX enzymes are expressed at low constitutive levels in the normal lung, a variety of factors may contribute to the up-regulation of COX-2 in the developing lung cancer environment. This leads to enhanced production of deleterious PG products, including prostaglandin E2 (PGE2), which has well-established promalignant effects. Contributors to persistent elevation of COX-2 in epithelial stromal and lung cancer cells include cytokines such as interleukin (IL)-1β and transforming growth factor β, growth factors including epidermal growth factor, oncogenic events such as mutant Kras or loss of p53, hypoxia, and tobacco-specific carcinogens (6–9). Once COX-2 is up-regulated in lung cancer cells, its elevation may be maintained by abnormalities in signaling pathways required to down-regulate COX-2. Two such abnormalities are loss of IL-10 receptor expression and constitutive nuclear localization of signal transducers and activators of transcription 6 (10, 11). Chemotherapy including taxanes also can stabilize COX-2 mRNA, thus leading to its prolonged and unregulated expression (12).

In lung cancer development and progression, elevations of COX-2 and PGE2 are driving forces for the hallmarks of malignancy including apoptosis resistance (13), proliferation (14), immunosuppression (15), angiogenesis (16), invasion (17), and epithelial-mesenchymal transition (18). These findings led to lung cancer chemoprevention trials using COX-2 inhibitors. Although some encouraging preliminary results are available from these trials (19, 20), several problems with COX-2 inhibitors likely will limit their widespread use in cancer chemoprevention. First, the potential risk of cardiovascular toxicities associated with the long-term use of COX-2 inhibitors may prove to be prohibitive for many individuals in the setting of chemoprevention. Second, in addition to inhibiting PGE2 production, the upstream blockade of COX-2 has the capacity to decrease PGs such as PGI2 and PGD2 that have been found to have antitumor properties (21). Similarly, the inhibition of COX-2 could result in increases in leukotrienes that have protumorigenic capacity (22). In some settings, therefore, the sword of COX-2 inhibition may be too blunt to specifically attack the tumor-promoting activities of the arachidonic acid pathway, and new approaches will be required to target the pathway downstream of COX-2 for lung cancer prevention.

Instead of directly inhibiting COX-2, it has been suggested that hitting downstream targets in the COX pathway may be more effective and less toxic for lung cancer chemoprevention (23). One downstream opportunity involves targeting the receptors whereby PGE2 mediates its tumor-promoting effects. PGE2 exerts its multiple effects through four G-protein-coupled receptors, designated as E-type PG (EP) receptors 1 through 4 (24). Response to PGE2 depends on the concentration and distribution of cell-surface EP receptors. The EP1 receptor acts via Gαi protein to increase cellular Ca2+ level. EP2 and EP4 receptor signaling is mediated by Gβγ proteins that activate adenylate cyclase and elevate cyclic AMP synthesis. In
contrast, EP3 receptor signaling through G, inhibits adenylate cyclase and cyclic AMP synthesis (24).

Studies suggest that PGE2 mediates lung cancer invasiveness through EP4 receptor signaling and that genetic inhibition of tumor COX-2 leads to diminished invasion, likely due to reduced expression of matrix metalloproteinase-2, CD44, and EP4 receptor (17). These findings indicate that PGE2 regulates COX-2–dependent CD44 and matrix metalloproteinase-2–mediated invasion in lung cancer via EP receptor signaling (17). In a murine model, Yang et al. (25) revealed that tumor metastasis to the lung was significantly reduced by treatment with a specific EP4 antagonist or when EP4 receptor expression was knocked down (via RNA interference) in tumor cells. In addition, metastasis and tumor growth are reduced in EP4 receptor knockout animals (25). The proliferation of human lung carcinoma cells following stimulation of the EP4 receptor provides further evidence of the role of E-type prostanoid receptors in lung carcinogenesis (26). Although blocking PGE2 activity by targeting the EP4 receptor was effective in these preclinical models, studies also reveal that different EP receptor subtypes may mediate different malignant phenotypes. For example, lung cancer invasion may be mediated by the EP4 receptor whereas the proliferative response may be promoted by EP1 receptor signaling (27). Defining the contribution of the EP receptors in mediating procarcinogenic events will require further investigations in model systems relevant to chemoprevention.

Another opportunity to suppress lung carcinogenesis via targets downstream of COX-2 is to promote increased PGE2 metabolism and clearance. The catabolic enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH), recently identified, is known to have tumor suppressor activity (28, 29), converts PGE2 to inactive 15-keto derivatives (30). Although the 15-keto derivatives are not active in mediating EP receptor–dependent signaling, they have recently been reported to have peroxisome proliferator-activated receptor-γ ligand activity and therefore could promote antitumor responses (31). Preventing the expression of 15-PGDH limits the degradation of PGE2, allowing it to accumulate and thus encouraging tumor growth (28). Therefore, augmenting 15-PGDH expression could lower PGE2 concentrations and carcinogenic effects in the developing tumor microenvironment.

In this issue of the journal, Hughes et al. (32) contribute important new information in their report “NAD+-Dependent 15-Hydroxyprostaglandin Dehydrogenase Regulates Levels of Bioactive Lipids in Non–Small-Cell Lung Cancer.” They found that 15-PGDH is commonly down-regulated in non–small-cell lung cancer (NSCLC) relative to normal lung, an effect that contributes to the accumulation of procarcinogenic PGs in NSCLC. The strength of these findings is the use of human tissues and corroboration in complementary in vitro and in vivo studies documenting that the enhanced levels of procarcinogenic PGs in NSCLC are a consequence of down-regulation of 15-PGDH. Recent studies corroborate the importance of these findings. Huang et al. (33) found that the forkhead transcription factor hepatocyte nuclear factor 3β is a potent transcriptional inducer of 15-PGDH, which showed tumor suppressor and antiangiogenic functions in vivo.

The findings of Hughes et al. provide further strong justification to pursue a novel avenue for attacking the arachidonic acid pathway in the context of lung cancer prevention. Targeted intervention that promotes the degradation of the procarcinogenic PGs including PGE2 could lead to a more favorable pulmonary environment in the lung at risk for carcinogenesis. Elevating 15-PGDH could increase the ratio of antitumorigenic to procarcinogenic PGs. For example, a decline in PGE2 without alteration of PGF2 levels could favor antitumorigenic effects as well as limit cardiovascular toxicities that might be associated with COX-2 inhibitors.

Recent reports help explain decreased 15-PGDH in breast and lung cancers. Wolf et al. (29) reported that 15-PGDH is epigenetically silenced in breast cancer, and Yang et al. (34) found that Zeb1 and Slug, members of the zinc-finger E-box binding transcriptional repressor family, repress 15-PGDH promoter activity in NSCLC. The latter finding is particularly interesting because mediators of inflammation including IL-1β and PGE2 have recently been found to induce the expression of certain members of this family of transcriptional repressors including Snail, Slug, and Zeb-1 (18, 35). This suggests that inflammatory mediators known to be abundant in the at-risk lung may contribute to the suppression of 15-PGDH. Furthermore, because PGE2 has the capacity to promote these transcriptional repressors, which then decrease 15-PGDH, a procarcinogenic self-enhancing process could be operative in the developing lung tumor environment. The capacity for cytokines such as IL-1β to induce membrane PGE synthase 1 could also contribute to these effects (36).

Although mutations in hydroxyprostaglandin dehydrogenase (HPGD; encoding 15-PGDH) have not been described in lung cancer, a recent report by Uppal et al. (37) describes HPGD mutations in primary (idiopathic) hypertrophic osteoarthropy. These mutations led to decreased 15-PGDH activity and increased systemic PGE2. Although not studied by Uppal et al., the common secondary form of this disease, often referred to as pulmonary hypertrophic osteoarthropy including digital clubbing, is closely associated with pulmonary diseases and intrathoracic malignancies. Further studies will be required to determine if pulmonary hypertrophic osteoarthropy is associated with decreased 15-PGDH due to either HPGD mutations or epigenetic silencing. The normal lung seems to be the major site of 15-PGDH activity and therefore PG deactivation (38). Therefore, pulmonary diseases, including those with the greatest risk for lung cancer, may have limitations in their capacity for PGE2 deactivation (39, 40). Additional research will be required to determine if this particular potential pulmonary “insufficiency” exacerbates the problem of the overproduction of PGE2 in at-risk lung tissue.

Because 15-PGDH has been described as having tumor suppressor activities in lung cancer (28, 41), investigators have asked if the levels and/or activity of 15-PGDH can be manipulated pharmacologically. Recent studies indicate that histone deacetylase inhibitors (42), steroids (41), epidermal growth factor receptor inhibitors (34), and thiazolidinediones (43) have the capacity to increase 15-PGDH. Although all of these agents are being considered for lung cancer chemoprevention, developmental work is still needed, including studies to define subgroups of at-risk individuals and to develop preventive agents targeting this pathway.
Understanding the events downstream of COX-2 in the arachidonic acid pathway in the context of pulmonary carcinogenesis will facilitate new opportunities for targeted intervention. For example, additional downstream targets, including the recently described PG transporters in colon cancer, may also be discovered to be operational in the pathogenesis of lung cancer (44). The work of Hughes et al. (32) is a significant contribution to our understanding of the downstream events and the complexities of pulmonary carcinogenesis and provides new insights for future chemoprevention.

Disclosure of Potential Conflicts of Interest

S. Dubinett serves on the scientific advisory board for Tragara Pharmaceuticals.

References

Focusing Downstream in Lung Cancer Prevention: 15-Hydroxyprostaglandin Dehydrogenase

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