Combined Targeting of the Epidermal Growth Factor Receptor and Cyclooxygenase-2 Pathways

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Extensive evidence implicates both the epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2) in carcinogenesis. Stimulation of EGFR signaling or enhanced synthesis of COX-2–derived prostanoids can influence several processes that are linked to carcinogenesis, including cell proliferation, apoptosis, angiogenesis, and invasiveness. These findings have provided the underpinnings for developing agents targeting EGFR or COX-2. Recent evidence of crosstalk between EGFR and COX-2 strengthens the rationale for combination regimens aimed at both targets. The promise of this approach is highlighted by the report of Zhang et al. (1) in this issue of Clinical Cancer Research.

Figure 1 illustrates major aspects of the interactive signaling between EGFR and COX-2. Activation of EGFR signaling leads to increased mitogen-activated protein kinase activity, resulting in activator protein-1–mediated induction of COX-2 transcription and enhanced synthesis of prostaglandin E2 (PGE2; ref. 2). Recent data show that stimulation of EGFR signaling also inhibits the expression of 15-hydroxyprostaglandin dehydrogenase, which is a key enzyme for the catabolism of PGE2 (3) and is suppressed in several tumor types (3–5). Therefore, the increased levels of PGE2 that occur in tumors likely result from the increased synthesis and reduced degradation of PGE2.

Considerable evidence indicates that COX-2–derived PGE2 can activate EGFR signaling and thereby stimulate cell proliferation (6). The mechanism(s) by which this occurs seem to be complex and context specific. PGE2 can stimulate matrix metalloproteinase activity, resulting in the shedding of active EGFR ligand from the plasma membrane, which in turn leads to increased EGFR signaling and enhanced DNA synthesis (7). PGE2 treatment can stimulate the cyclic AMP–protein kinase A→cyclic AMP-responsive element binding protein signaling pathway, which increases the expression of the EGFR ligand amphiregulin (Fig. 1; ref. 8). Transactivation of EGFR by PGE2 can be mediated by an intracellular Src-dependent mechanism that is independent of the release of extracellular ligands of EGFR (9). Regardless of the precise mechanism for doing so, exposure to COX-2–derived PGE2 can initiate a positive feedback loop whereby activation of EGFR results in enhanced expression of COX-2 and increased synthesis of prostaglandins. This leads in turn to a further increase in EGFR activity.

Crosstalk between EGFR and COX-2 may be important for tumor invasion, metastasis, and the epithelial-to-mesenchymal transition (EMT; Fig. 2). EMT involves dedifferentiation of epithelial cells to fibroblastoid migratory cells with a markedly altered mesenchymal gene expression profile. E-cadherin plays a key role in epithelial intercellular adhesion (Fig. 2), and down-regulation of E-cadherin is a hallmark of EMT (10). Reduced expression of E-cadherin in human tumors is associated with invasion, metastasis, and decreased survival (11). These findings are consistent with recent data showing that suppressed E-cadherin expression can lead to the development of a highly aggressive squamous cell cancer phenotype (12). Several findings suggest that EGFR signaling and COX-2–derived PGE2 play a role in EMT. Chronic EGF treatment disrupts cell-to-cell adhesion, suppresses expression of E-cadherin, and causes EMT in human tumor cells overexpressing EGFR (13). These effects are a consequence, at least in part, of EGF-mediated induction of the transcriptional repressor Snail, a known inhibitor of E-cadherin transcription. Changes in levels of COX-2 also can affect levels of E-cadherin. As reported ~10 years ago, overexpression of COX-2 in intestinal epithelial cells can suppress the expression of E-cadherin and enhance adhesion to extracellular matrix (14). This COX-2–mediated change in cell phenotype was reversed by treatment with sulindac sulfide, a COX inhibitor. Recently, this work was extended to non–small-cell lung cancer. Overexpression of COX-2 or treatment with exogenous PGE2 significantly decreased the expression of E-cadherin and led to a reduction in cell aggregation (15). The transcriptional suppressors of E-cadherin, ZEB1 and Snail, were up-regulated in non–small-cell lung cancer cells that overexpressed COX-2 or were treated with PGE2 (Fig. 2). The ability of treatment with either EGF or PGE2 to induce Snail and suppress E-cadherin underscores the strong potential of pharmacologically targeting crosstalk between EGFR and COX-2 for cancer prevention and therapy.

In a recent study of non–small-cell lung cancer, cells expressing E-cadherin were more sensitive to growth inhibition by erlotinib, an inhibitor of EGFR tyrosine kinase, than were cells that had lost E-cadherin expression and gained the expression of mesenchymal markers (e.g., vimentin; refs. 16, 17). This intriguing finding suggests that the EMT status of a tumor may help determine its responsiveness to EGFR-targeted therapies. Because COX-2–derived PGE2 can suppress levels of E-cadherin, it is possible that treatment with a COX-2 inhibitor will induce E-cadherin levels and thereby sensitize
tumor cells to growth inhibition by agents targeting EGFR (Fig. 2). This hypothesis has not yet been, and should be, evaluated in humans. Targeting EMT also could reduce the metastatic potential of tumors. Such targeting could include EGFR and/or COX-2 inhibitors in combination with compounds such as matrix metalloproteinase inhibitors that can modulate the migration, invasion, and/or proliferation of mesenchymal cells.

We have emphasized the significance of crosstalk between EGFR and COX-2 in carcinogenesis. It is also important to stress that EGFR and its downstream effectors can be activated independently of COX-2/PGE2. Similarly, COX-2/PGE2 and its downstream effectors can be regulated independently of EGFR signaling. For example, PGE2 can stimulate cell proliferation by an EGFR-independent mechanism (18). These mutually independent effects further support a combinatorial approach targeting both EGFR and COX-2, which has strong preclinical support as well. Torrance et al. (19) tested the effects of a dual inhibitor of COX-1/COX-2 combined with an inhibitor of EGFR tyrosine kinase on the number of adenomas that develop in ApcMin mice. This combination regimen almost completely prevented adenoma development in Apc Min mice, which normally develop numerous intestinal polyps as a result of a mutation in the APC tumor suppressor gene. Zhang et al. (1) showed that combining gefitinib, an EGFR tyrosine kinase inhibitor, with celecoxib, a selective COX-2 inhibitor, was more effective than either agent alone in suppressing the growth of experimental head and neck squamous cell carcinoma. Inhibition of tumor growth was associated with reduced levels of phospho-EGFR, extracellular signal-regulated kinase/mitogen-activated protein kinase activity, phospho-signal transducers and activators of transcription 3, vascular endothelial growth factor, and Ki-67.

The EGFR—COX-2 interaction highlights the molecular interface between cancer therapy and cancer prevention and the growing convergence of molecular targeted approaches for both (20). The independent and interactive signaling of EGFR and COX-2 has been shown in many sites of carcinogenesis, including the lung, bladder, and oral cavity. A recently reported trial of combined EGFR and COX-2 inhibitors in non-small-cell lung cancer patients produced promising safety and activity results (21). Our group and others are in advanced stages of developing trials of combined EGFR and COX-2 inhibitors to prevent oral cancer in very high-risk dysplastic oral leukoplakia patients such as those with aneuploid lesions. The data suggesting that COX-2 inhibitors may potentiate (by up-regulating E-cadherin) the activity of EGFR inhibitors in preventing or reversing EMT could be very relevant to prevention in the setting of aneuploid dysplastic leukoplakia because these lesions have
high rates of aggressive, multifocal disease implying traits (e.g., cell migration, motility, and metastasis) associated with EMT (22–24). This combination in aneuploid dysplastic leukoplakia patients will be used at relatively high doses of each inhibitor because the very high cancer risks of aneuploidy justify the potential risks of side effects such as the increased cardiovascular disease associated with COX-2 inhibitors. Combinations with lower individual doses may be justified in lower-risk settings (e.g., dysplastic leukoplakia without aneuploidy) because of the potential to retain efficacy (although the independent and interactive effects of each agent could be lessened) and to reduce cardiovascular and other potential toxicity. Combined targeting of EGFR and COX-2 has entered the spotlight of clinical testing for cancer prevention and therapy and shows great promise for reducing the burden of cancer in many sites.

Fig. 2. Interactive signaling pathways that influence the EMT. In this model, overexpression of COX-2 induces the transcriptional repressors ZEB1 and Snail, leading to reduced levels of E-cadherin. These changes help to drive the transition of an epithelial cell to a mesenchymal-like phenotype (EMT). Treatment with the selective COX-2 inhibitor celecoxib can potentially reverse this phenomenon, or induce MET, and thereby sensitize tumor cells to the growth inhibitory effects of erlotinib, an inhibitor of EGFR tyrosine kinase.

References
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