Cyclooxygenase-2 Inhibitor Therapy for the Prevention of Esophageal Adenocarcinoma in Barrett’s Esophagus

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The outcome for patients diagnosed with esophageal adenocarcinoma remains abysmal despite a better understanding of the molecular events that underlie development of the disease. Additionally, the incidence for this type of esophageal carcinoma has been rapidly increasing in the United States over the last three decades (1). Esophageal adenocarcinoma often occurs in the setting of Barrett’s esophagus, a condition caused by chronic gastroesophageal reflux, which is characterized histologically by a transition of the squamous cell mucosa of the distal esophagus to metaplasticcolumnar epithelial cells (2). Patients with Barrett’s esophagus are clearly at increased risk for developing esophageal adenocarcinoma. A potentially effective approach to reducing morbidity and mortality from this cancer would be a prevention program that slowed or even stopped the metaplastic transition in Barrett’s patients early in the disease process. One potential candidate for preventive therapy is a combination of antireflux agents and nonsteroidal anti-inflammatory drugs (NSAIDs). However, a strong rationale for using NSAIDs has been lacking due to the relative paucity of data examining the effects of these drugs on the growth of Barrett’s esophageal cells. In this issue of the Journal, Buttar et al. (3) offer a scientific underpinning for the use of NSAID therapy in Barrett’s patients by demonstrating that selective inhibitors of the cyclooxygenase-2 (COX-2) enzyme inhibit the growth in vitro of cells isolated from the mucosa of Barrett’s esophagus.

Since Waddell and Loughry’s initial discovery that the NSAID sulindac reduced the growth of rectal polyps in patients with Gardner’s syndrome, evidence has mounted that this class of compounds is effective in the prevention of colorectal cancer [for review, see (4)]. NSAIDs are thought to inhibit colorectal cancer cell growth primarily through the inhibition of COX-2, although other non-COX biochemical targets of NSAIDs may also be involved. Evidence supporting this notion includes the facts that COX-2 levels are aberrantly elevated in colorectal cancers; that specific inhibitors of COX-2 (the new "coxib" family of drugs) are potent inhibitors of intestinal polyp growth in both animal models and humans with the hereditary polyposis syndrome, familial adenomatous polyposis (FAP); and that intestinal polyp growth is severely limited in mice genetically null for COX-2.

It is now apparent that COX-2 may play a pro-oncogenic role in a range of extracolonic cancers, including esophageal cancer. Several groups (5–7) have reported that COX-2 levels are increased in Barrett’s esophagus and associated adenocarcinoma. Moreover, the level of expression correlates with the degree of dysplasia; higher levels of COX-2 protein were detected in high-grade dysplasia and adenocarcinoma tissue than in benign or low-grade dysplasia (6). The stimulus for induction of COX-2 during the chronic gastroesophageal reflux, characteristic of Barrett’s esophagus, may be because of bile acids found in duodenal contents and the high concentration of proinflammatory cytokines present in the ulcerated esophageal mucosa (8,9). Finally, there is evidence that elevated COX-2 activity plays a functional role in the growth of esophageal adenocarcinoma. Two different esophageal adenocarcinoma cell lines that express high levels of COX-2 protein are growth suppressed in the presence of a COX-2, but not a COX-1, selective inhibitor (10). The decrease in cell growth was associated with an increase in the levels of apoptosis. By contrast, a selective COX-2 inhibitor had no effect on the growth of an esophageal adenocarcinoma cell line that did not express COX-2 protein.

This last study (10) suggests that COX-2 inhibitors may be useful therapy for esophageal adenocarcinoma. However, no information was previously available concerning whether COX-2 inhibitors block the growth of epithelial cells isolated directly from Barrett’s esophageal epithelium. Buttar et al. (3) addressed this issue by examining the effects of a COX-2 inhibitor on primary esophageal cell lines established from endoscopic biopsy specimens taken from patients with Barrett’s esophagus. Treatment of this Barrett’s esophageal cell line with the selective COX-2 inhibitor NS-398 at 50 μM caused a decrease in cellular proliferation of 55% compared with control cells. This effect is likely the result of the specific inhibition of COX-2 enzymatic activity, because the addition of exogenous prostaglandin (PG) E2 reversed the antiproliferative effect of NS-398.

Although these results are potentially exciting because they imply that treatment with COX-2 inhibitors might stem the transition from Barrett’s epithelium to esophageal adenocarcinoma, several important questions remain unanswered. First, this study was exclusively limited to cultured cells, and it will be important to determine whether the findings can be replicated in an in vivo model system. In mice or rats, surgical induction of esophageal reflux by esophagojejunostomy followed by treatment with the carcinogen N-methyl-N-benzylnitrosamine (MBN) will cause the development of Barrett’s esophagus and Barrett’s-associated adenocarcinoma (11). It will be critical to determine whether treatment with a selective COX-2 inhibitor can block the development of esophageal adenocarcinoma in this model. Second, several studies have demonstrated that COX-2 may play an important role in the wound-healing response in the mucosa of the gastrointestinal tract, because experimentally induced ulceration in the stomach (12) or colon (13) of mice is exacerbated by treatment with a COX-2 selective inhibitor. Thus, a major

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concern will be to determine whether the inhibition of COX-2 might paradoxically enhance the level of ulceration, inflammation, and metaplasia in a mouse model of Barrett’s esophagus. Finally, more research must be done on the downstream PG signaling pathways involved in Barrett’s epithelial cell lines. The major PG metabolite of these cells, PGE2, can bind to four distinct G-protein-coupled cell surface receptors (EP1–EP4). Genetic studies using mice lacking each of the EP receptors have implicated the EP2 receptor in the promotion of intestinal polyposis (14). It will be essential to determine which EP receptor(s) are responsible for the pro-proliferative effect of PGE2 on esophageal epithelial cells, because specific EP receptor antagonists are being developed that may offer therapeutic advantages over COX-2 inhibitor therapy. In summary, although much more work remains to determine whether COX-2 inhibitor therapy will be useful in the treatment of Barrett’s patients, the present study by Buttar et al. (3) is a key first step that provides the impetus for further investigations in this important area.

REFERENCES


