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COX-2 and Colon Cancer: Potential Targets for Chemoprevention

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Abstract Evidence derived from several lines of investigation suggest that prostaglandins, metabolites of arachidonic acid, play an important role in colon cancer development. Elevated prostaglandin levels are found in colon cancers and their precursor lesions, adenomatous polyps. Agents such as aspirin and NSAIDs, which inhibit the generation of these arachidonic acid metabolites, are associated with a decreased risk of developing or dying from colon cancer. Both the amount of the agent used and the duration of exposure seem to be important variables. In animals, NSAIDs are among the most potent agents discovered for the reduction of tumors in both genetic and carcinogen-induced models. Data from human trials also suggests that NSAIDs such as sulindac can reduce the size and number of polyps in individuals with familial adenomatous polyposis (FAP). In parallel with the above findings, it is now understood that at least two forms of the enzyme responsible for the metabolism of arachidonic acid exist. One of these forms, COX-1, is generally considered a constitutive form that is responsible for maintaining normal physiologic function. Inhibition of COX-1 leads to many of the clinically undesirable side effects associated with NSAID use. The other known form of the enzyme, COX-2, is an inducible form that is found in increased levels in inflammatory states and in many cancers and their associated pre-malignant lesions. Levels of COX-2 are increased by exposure to mitogens and growth factors. Agents that specifically inhibit COX-2 are now in clinical development and appear to be well-tolerated and effective for the treatment of osteoarthritis and rheumatoid arthritis. The potential for use of COX-2 specific NSAIDs in the prevention of colon cancer is suggested from the distribution of COX-2 in adenomatous polyps and colon cancer and the effectiveness of these agents in genetic and carcinogen-induced animal models of colon cancer. The development of these agents for the prevention of colon cancer will be discussed. J. Cell. Biochem. Suppl. 34:97–102, 2000.

Key words: NSAID; prostaglandin; cyclooxygenase; arachidonic acid; cancer prevention

Nearly 160,000 new cases of colorectal cancer are diagnosed in the United States each year resulting in as many as 60,000 deaths (American Cancer Society, 1994). Although colon cancer can be cured if treated in the early stages, current screening measures such as fecal occult blood testing and sigmoidoscopy have only reduced mortality rates by one-third [Weiss and Forman, 1996]. As such, many recent research efforts have focused on improving screening techniques and developing colon cancer prevention strategies.

According to the work of Fearon and Vogelstein [1990], colorectal tumors arise as a result of the accumulation of genomic alterations, including somatic or germline mutations which result in the activation of oncogenes, the inactivation of suppressor genes, and the activation of mutator genes. Development of colorectal cancer begins with hyperproliferation of the colonic epithelial mucosa, followed by formation and the evolution of adenomatous polyps, and finally adenocarcinoma. Presently, it is thought that more than 95% of colorectal adenocarcinomas arise from adenomatous polyps. Because the development of malignant disease in humans requires an average of 15 to 25 years, a significant time period during which intervention measures could be applied exists. This time and multi-step process of carcinogenesis is thus amenable to regional or systemic pharmacologic interventions. Populations for which the risk/benefit analysis could be analyzed for include the full spectrum from apparently healthy subjects at a background cancer risk, to subjects at intermediate cancer risk due to individual lifestyle choices (e.g., diet, tobacco use)

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or environmental or occupational exposure to carcinogens, to subjects or patients at high risk due to genetic predisposition (e.g., FAP, HNPCC), existing precancerous lesions, or prior invasive cancers.

Prostaglandins and Cancer

In 1930, American gynecologists Kurzrok and Lieb observed that strips of human uterus relax or contract when exposed to human semen [Campbell and Halushka, 1996]. Within a few years, von Euler and Goldblatt independently reported that smooth muscle-contracting and vasodepressor activity was found in seminal fluid and accessory reproductive glands [von Euler, 1973]. Von Euler identified the active substance as a lipid soluble acid which he named "prostaglandin" (PG). Since that time, a host of PGs, 20-carbon unsaturated carboxylic acids with a cyclopentane ring, have been identified in various tissues throughout the body. Prostaglandins have long been associated with mechanisms involved in the protection of organ integrity and function. Among their many roles, PGs are important in the maintenance of normal gastrointestinal and kidney function. Over the past few decades, however, a link between cancer development, cancer progression, and invasiveness, and PGs has been reported [Lupulescu, 1996]. Elevated PG concentrations were first associated with cancer in 1968 [Williams et al., 1968] when increased PGE_2 and $PGF_{2\alpha}$ levels were observed in tumor tissue and blood of patients with medullary carcinoma of the thyroid. During the ensuing years, several studies reported increased circulating levels of PGs in the blood of patients with Kaposi's sarcoma [Bhana et al., 1971], breast cancer [Bockmann and Meyers, 1977], renal cell carcinoma [Cummings and Robertson, 1977], bronchial carcinoma [Fiedler et al., 1980], and other cancers. Recently, investigators [Rigas et al., 1993] observed significantly increased PGE_2 levels within the colon cancer tissue of twenty one human patients, but not in normal mucosa samples 5–10 cm away from the tumor biopsies. Subsequent experiments have confirmed these findings [Eberhart et al., 1994; Kargman et al., 1995; Sano et al., 1995; DuBois et al., 1996] indicating that both COX-2 and PGE_2 levels are also increased within intestinal adenomatous polyps. The observation that COX-2 and PGE_2 levels are increased at this relatively early step in the pathway to cancer may render them amenable to pharmacologic intervention.

Although the precise relationship between COX expression, PG production, and colon cancer is not clearly understood, reports suggest that over-expression of COX-2 leads to PG-mediated resistance to apoptosis, enhanced expression of BCL-2, and decreased expression of both E-cadherin and transforming growth factor β2 (TGFβ2) receptor [Tsujii and DuBois, 1995]. E-cadherin is involved in cell-cell adhesion and TGFβ2 receptors transduce signals important in modulating programmed cell death. Additionally, PGE_2 induces cellular proliferation [Denizot et al., 1993] and, at high levels, may also suppress immune surveillance and killing of malignant cells [Plescia et al., 1975; Balch et al., 1984]. In cells with mutated *Apc* genes, continuously elevated levels of PGs can also lead to the desensitization and down-regulation of adenylate cyclase, uncoupling of cAMP synthesis from prostaglandin, and inactivation of protein kinase A (PKA), mechanisms normally important for cell-cell communication, adherence, and the phosphorylated cell state needed for such functions [Waddell and Miesfeld, 1995]. Cyclooxygenase may also play a direct role in carcinogenesis through the enzymatic activation of procarcinogens to electrophiles that form DNA adducts [Earnest et al., 1992].

In contrast, a recent report by Chan et al. [1998] suggests that mechanisms underlying NSAID-mediated apoptosis may not be related to a reduction in prostaglandins, but rather may be due to the elevation of the prostaglandin precursor arachidonic acid. As observed in vitro, NSAID treatment of colon tumor cells results in a dramatic increase in arachidonic acid that in turn stimulates the conversion of sphingomyelin to ceramide, a known mediator of apoptosis. It may be noteworthy, however, that NSAID concentrations used in this experiment greatly exceeded levels needed to observe clinical effects.

NSAIDs and Colon Cancer

Because the primary anti-inflammatory property of NSAIDs is inhibition of the cyclooxygenase enzymes and, consequently, lowered levels of PGs, NSAIDs have been hypothesized to play a role in reducing cancer incidence. Three primary lines of evidence suggest that NSAIDs are protective for colon cancer. First, as reviewed

by Giardiello et al. [1995], several large-scale epidemiologic studies indicate a 40–50% reduction in mortality from colorectal cancer in individuals who take NSAIDs on a regular basis compared with those who do not. Importantly, the protective effects seen in many of these studies increase with greater duration of use and persist even after known colon cancer risk factors are controlled for, suggesting a causal relationship. A limitation of these reports, however, is that only incomplete information on dose, duration of use and potentially confounding lifestyle factors was attainable. Second, the chemopreventive efficacy of NSAIDs against colon cancer is supported by animal studies. The NSAIDs aspirin, piroxicam, sulindac, naproxen, ketoprofen, indomethacin, and ibuprofen reduced both the number and size of carcinogen-induced colon tumors in rodent models, even in some cases when administered months after exposure to carcinogen and when microscopic tumors were already present [Giardiello et al., 1995]. Piroxicam and sulindac have also inhibited colon carcinogenesis in the Min mouse, an animal model harboring a nonsense mutation in the *Apc* gene resulting in a phenotype similar to that seen in patients with FAP [Jacoby et al., 1996; Beazer-Barclay et al., 1996; Boolbol et al., 1996].

Third, in several uncontrolled and controlled clinical studies, patients with FAP experienced significant regression of polyps when treated with sulindac. In the first of these trials, Waddell and Loughry [1983] reported that 75–150 mg sulindac BID caused a 70–100% regression of rectal adenomatous polyps in four patients with FAP. In 1991, Labayle et al. [1991] performed the first randomized, placebo-controlled, double-blinded, crossover study in nine FAP patients with ileorectal anastomosis [Labayle et al., 1991]. Three-hundred mg of sulindac per day caused complete polyp regression in six patients and a partial regression in the remaining three in less than 4 months. Cessation of sulindac treatment resulted in polyp recurrence. Two years later, Giardiello et al. [1993] conducted a randomized, double-blinded, placebo-controlled trial in 22 patients with FAP. Patients receiving 300 mg per day sulindac for 9 months had decreased polyp incidence by 44% of baseline levels ($P = 0.014$) and decreased polyp size by 35% ($P = 0.001$).

COX-2 and Colon Cancer

Current research indicates that the enhanced synthesis of PGs seen in intestinal tumors is a result of COX-catalyzed metabolism of arachidonic acid. To date, two forms of the cyclooxygenase enzyme have been identified. The COX-1 isoform, first purified in 1976, is expressed constitutively throughout normal human and rodent tissues, including the kidney and gastric mucosa, where the PGs produced are thought to play a protective role. In 1991, a second, inducible isoform of the cyclooxygenase enzyme, COX-2, was identified and cloned. Unlike COX-1, COX-2 expression is affected by various stimuli including mitogens, growth factors, oncogenes, and tumor promoters and recent evidence suggests that it may be involved in the conversion of a cell from normal to malignant. As previously mentioned, COX-2 expression is increased in human colorectal polyps compared to adjacent normal mucosa. COX-2 protein formation also parallels the increase in prostaglandin production after stimulation with mitogens or tumor promoters in a wide variety of cell types in mice [Williams et al., 1997]; striking elevations of COX-2 mRNA and protein have been observed in intestinal tumors in rodents after carcinogen treatment [DuBois et al., 1996] and in adenomas from Min mice [Williams et al., 1996]. Interestingly, COX-2 was absent from the normal appearing mucosa in these animals. Moreover, when intestinal epithelial cells are forced to express COX-2 constitutively, they develop an altered phenotype including changes in their adhesion properties and a resistance to apoptosis—characteristics that are consistent with increased tumorigenic potential [Tsujii and DuBois, 1995]. Recently, investigators demonstrated a 40% reduction in aberrant crypt formation in carcinogen-treated rats given celecoxib (SC-58635), a specific COX-2 inhibitor [Reddy et al., 1996]. In a subsequent experiment, dietary administration of celecoxib decreased both the incidence and multiplicity of azoxymethane- (AOM) induced colon tumors by about 93% and 97%, respectively, and decreased overall tumor burden by more than 87% [Kawamori et al., 1998]. Only two (6%) out of 36 rats that received celecoxib displayed tumors in the colon while 29 of the rats treated with AOM and fed control diets developed colonic tumors. Importantly, long-term administration of celecoxib at 1,500 ppm did not induce any toxic side

effects such as body weight loss, gastrointestinal ulceration, or bleeding. COX-2 expression and intestinal tumor promotion have also been directly linked via a COX-2 knockout model. $Apc^{\delta 716}/+$ mice, which develop hundreds of tumors per intestine, bred with COX-2 null mice have a 80–90% reduction in tumor multiplicity in the homozygous COX-2 null offspring [Oshima et al., 1996]. In addition, the use of MF tricyclic, a specific COX-2 inhibitor, was more effective than sulindac and nearly as effective as the COX-2 knockout at inhibiting intestinal polyps [Oshima et al., 1996]. Moreover, Jacoby et al. [1998] reported that celecoxib caused adenoma regression in the *Apc* mutant Min mouse model. In this experiment, celecoxib substantially and significantly decreased tumor multiplicity. Microscopic examination of the intestinal mucosa of animals demonstrated changes consistent with regression of existing disease. These results, in toto, suggest that 1) the COX-2 enzyme may act as a tumor promoter in the intestine, 2) that increased COX-2 gene expression may result from disruption of the *Apc* gene, and 3) that specific inhibition of COX-2 is a plausible approach to cancer prevention.

While significant epidemiologic, in vitro, animal and human data suggest that NSAID use can reduce the incidence of certain cancers, their potential use as cancer prevention and/or treatment agents has been limited by gastrointestinal and renal toxicity associated with chronic intake. NSAIDs inhibit both COX-1 and COX-2, non-specifically. The resultant inhibition of COX-1 destroys the traditional "housekeeping" effects associated with this enzyme. The recent discovery that COX-1 and COX-2 have different structural binding sites for NSAIDs has led to the development of several specific inhibitors of COX-2—tight binding inhibitors that display time-dependent kinetics of inhibition. Such specific COX-2 inhibitors blocked carrageenan-induced inflammation in the footpad and air pouch of rats while causing no effect on gastric PG production [Seibert et al., 1994; Masferrer et al., 1994]. These results indicate that induction of COX-2 is responsible for the production of PGs at the site of inflammation, whereas the normal synthesis of PGs in the stomach appears to depend on constitutive COX-1 activity. In a recent 1-week, double-blind upper gastrointestinal study, six of 32 (19%) subjects receiving naproxen developed gastric ulcers; no ulcers occurred in subjects receiving celecoxib or placebo [Simon et al., in press]. Moreover, in a 14-day, two-period, open label platelet study, celecoxib had no meaningful effect on platelet aggregation measures and thromboxane B_2 levels. Conversely, aspirin caused significant decreases in two of three platelet aggregation measures and thromboxane B_2 levels. Because COX-2 and not COX-1 is elevated in colonic tumors and precursor lesions and because of the potential for an improved gastrointestinal, renal and platelet safety profile, specific COX-2 inhibitors are currently being tested as cancer chemopreventive agents in controlled clinical trials in patients with FAP and hereditary non-polyposis colorectal cancer (HNPCC). Although these populations have a genetic predisposition to colon cancer, a number of observations suggest that colorectal carcinogenesis is similar in both FAP and sporadic settings. Namely, colorectal adenomas and carcinoma develop primarily in the left colon in both settings. Prevention strategies which include serial surveillance and surgical interventions are effective in both settings and genetic analysis of biopsy tissue from sporadic and FAP-associated adenomas/carcinomas commonly show similar somatic mutations involving the *Apc* gene. Thus, although FAP accounts for only 1% of the colorectal cases in the U.S., prevention strategies involving this cohort appear applicable to the larger population of patients with sporadic colorectal adenomas and cancer.

Future Prospects

Despite the vast data suggesting that NSAIDs prevent colon cancer, many questions must still be answered before such therapy can be recommended for "at risk" populations. The specific roles of COX-1 and COX-2 in the pathogenesis of colon cancer need to be resolved. It is not clear whether the inhibition of COX-1, COX-2 or both isoforms is essential to the preventive effects of aspirin and other NSAIDs on colon cancer incidence. It has been speculated that NSAIDs can induce apoptosis via a non-prostaglandin mediated pathway (sulindac sulfone) or through increases in arachidonic acid with a resultant conversion of sphingomyelin to ceramide [Chan et al., 1998].

As specific COX-2 inhibitors will likely be safer than non-specific NSAIDs, trials with celecoxib have been initiated in human subjects at risk for developing colon cancer. Such studies

will indicate whether or not COX-2 selective inhibitors can suppress formation of adenomatous polyps in the colon. This data will contribute significantly to our understanding of the relative importance of COX-2 inhibition for the prevention of colon cancer.

In addition to the use of COX-2 inhibitors as monotherapy, it has been suggested that optimal prevention strategies, as with cancer therapy, may require a combination of prevention agents. Employing COX-2 inhibitors with agents that act via different mechanisms of prevention may potentiate the preventive effects of either agent alone and expand the strategies available for those at high risk of developing cancer. As reviewed by Subbaramaiah and colleagues [1997], several investigators have observed that compounds including radicicol, genistein, curcumin, herbimycin A, and retinoids can inhibit Cox-2 gene expression. This suggests that specific, tumor-related pathways for up-regulating Cox-2 expression might be blocked selectively. Finally, as COX-2 levels are significantly increased in colonic polyps, specific inhibitors of the enzyme may also be considered in primary colon cancer treatment settings.

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