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The Role of COX-2 in Intestinal Inflammation and Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is a heterogeneous disease, including at least three major forms: hereditary, sporadic, and colitis-associated CRC. A large body of evidence indicates that genetic mutations, epigenetic changes, chronic inflammation, diet, and lifestyle are the risk factors for CRC. Since elevated cyclooxygenase-2 (COX-2) expression was found in most colorectal cancer tissue and is associated with worse survival among CRC patients, investigators have sought to evaluate the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors (COXIBs) on CRC prevention and treatment. The epidemiologic studies, clinical trials, and animal experiments indicate that NSAIDs are among the most promising chemopreventive agents for this disease. NSAIDs exert their anti-inflammatory and anti-tumor effects primarily by reducing prostaglandin production via inhibition of COX-2 activity. In this review, we highlight breakthroughs in our understanding of the roles of COX-2 in CRC and inflammatory bowel disease (IBD). These recent data provide a rationale for re-evaluating COX-2 as both the prognostic and the predictive marker in a wide variety of malignancies and for renewing the interest in evaluating relative benefits and risk of COX-2 inhibitors in appropriately selected patients for cancer prevention and treatment.

Keywords

cyclooxygenase; prostaglandins; NSAIDs; inflammation; colorectal cancer

Introduction

Cancer is the second-leading cause of death in United States and represents a significant health concern in most industrialized countries. A large body of evidence indicates that genetic mutations, epigenetic changes, diet, lifestyle, and chronic inflammation are risk factors for cancer. Currently, the most effective treatments for cancer, including various combinations of surgical resection, radiation, and/or chemotherapy, depend on the detection of cancer at a very early-stage. Unfortunately, it has not been possible to identify all individuals at the earliest stages of disease. In fact, most patients present to their physician with advanced cancer when standard treatments for solid malignancies result in a much lower 5-year survival. Thus, an effective approach for this disease must include prevention and targeted therapy. It is generally agreed that an effective way to control cancer is to find better ways of preventing it and/or detecting the disease at its earliest stage.

Colorectal cancer (CRC) is a heterogeneous disease. At least three major forms of CRC have been described: hereditary, sporadic, and colitis-associated CRC. Patients with familial

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adenomatous polyposis (FAP), due to a germ-line mutation in one allele of the tumor suppressor gene adenomatous polyposis coli (*APC*), have a near 100% risk of developing CRC by the age of 40 if untreated. Somatic loss of APC function occurs in about 85% of sporadic colorectal adenomas and carcinomas (Jen et al., 1994; Powell et al., 1992; Smith et al., 1994). Hereditary nonpolyposis colorectal cancer (HNPCC), which is due to inherited mutations in genes for DNA mismatch repair such as *MLH1*, *MSH2*, and *MSH6*, is responsible for approximately 2 to 7 percent of all diagnosed cases of CRC. The average age of patients with this syndrome develop cancer at around 44 years old, as compared to 64 years old in the general population.

Chronic inflammation and aging are other risk factors associated with CRC development. The gastrointestinal mucosa forms a complex semi-permeable barrier between the host and the largest source of foreign antigens. The mucosal immune system has the ability to mount an immune response to pathogens and also maintains tolerance to the vast array of benign luminal antigens from food and commensal bacteria. Many inflammatory processes are self-limiting, supporting the existence of endogenous anti-inflammatory mechanisms. In contrast, an abnormal mucosal immune response is thought to result in chronic inflammation such as inflammatory bowel disease (IBD). The IBD ordinarily affects over 5 million people between the age of 16 and 40 and causes significant morbidity in North American and Europe. The IBD is a complex class of immune disorders that has been grouped into two major forms, ulcerative colitis (UC) and Crohn's disease (CD). In general, CD has been traditionally considered to be Th1 (T helper) cell-mediated response, while UC is thought to be Th2-mediated response. However, a newly defined class of IL-17-producing $CD4^+$ T cells, termed Th17 cells, has been found to play a key role in CD and may alter the notion of this Th1 and Th2 dichotomy in IBD (Harrington et al., 2006; Steinman, 2007).

Together with the hereditary syndromes of FAP and hereditary nonpolyposis CRC, IBD is among the top three high-risk conditions for CRC. In particular, chronic IBD (especially pan-colitis) significantly increases the risk for developing CRC (Izzo and Camilleri, 2008; Lewis et al., 1999). Therefore, patients with IBD face an increased lifetime risk for developing CRC. Compared with sporadic CRC, colitis-associated CRC affects individuals at a younger age than the general population. Since dysplasia in patients with IBD can be polypoid or flat, localized, diffuse, or multifocal, syndromes of dysplasia in the colon indicate the entire colon as being at heightened risk of neoplasia. Unfortunately, the entire colon has to be surgical removed after detection of dysplasia in the colon. Therefore, clinical cancer surveillance in IBD patients is more challenging than in patients without IBD. Thus, an effective approach for this disease should consider chemopreventive approaches if proven beneficial.

Preventive effects of NSAIDs on CRC

A significant effort has been made to identify novel drug targets for CRC prevention and treatment. One group of compounds found to decrease the risk of CRC includes non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), which target the cyclooxygenase enzymes (COX-1 and COX-2). Although NSAIDs are some of the most commonly used drugs in the United States and around the world, the prolonged use of non-selective NSAIDs is associated with side effects such as nausea, dyspepsia, gastritis, abdominal pain, peptic ulcer, gastrointestinal bleeding and/or perforation of gastroduodenal ulcers (Wolfe et al., 1999). Since elevated COX-2 expression was found in approximately 50% of adenomas and 85% of adenocarcinomas (Eberhart et al., 1994; Gupta and DuBois, 2001; Marnett and DuBois, 2002) and is associated with worse survival among CRC patients (Ogino et al., 2008), it was hypothesized that NSAIDs exert some of their anti-inflammatory and anti-tumor effects through inhibition of the inducible COX-2 (Grover et al., 2003; Vane et al.,

1998). The unwanted side effects of these drugs as mentioned above were postulated to arise from the inhibition of the constitutive COX-1 (Vane, 1971). Therefore, investigators originally developed selective COX-2 inhibitors (COXIBs) such as celecoxib, rofecoxib, and valdecoxib in order to overcome the gastrointestinal adverse events of nonselective NSAIDs that placed limits on effective therapy.

A large body of evidence from population-based studies, case control studies, and clinical trials indicate that regular use of NSAIDs including aspirin and COXIBs over a 10–15 year period reduces the relative risk of developing CRC by 40–50% (Chan et al., 2008; Flossmann and Rothwell, 2007; Rostom et al., 2007). In particularly, aspirin specifically prevents the subgroup of patients whose colon tumors expressed COX-2 at higher levels (Chan et al., 2007). In addition to prevention, regular aspirin use after the diagnosis of CRC at stage I, II, and III improves overall survival, especially among individuals with tumors that overexpress COX-2 (Chan *et al*., 2009), suggesting the potential therapeutic use of NSAIDs in advanced CRC. A similar observation was obtained from advanced breast cancer patients treated with celecoxib (Fabi et al., 2008). Furthermore, a randomized double-blind trial showed that NSAIDs have preventive effects on patients with previous CRC (Bertagnolli et al., 2006; Sandler et al., 2003). These findings prompted investigators to evaluate the preventive effects and safety of COXIBs in patients with FAP or previous history of adenomas. The data from randomized/controlled trials, cohort and case-control studies demonstrated that long-term use of NSAIDs leads to the regression of preexisting adenomas in patients with FAP (Rostom et al., 2007). Particularly, the evidence that treatment of FAP patients with celecoxib significantly reduced the polyp burden in a randomized controlled trial led to the FDA approving celecoxib (brand name Celebrex) for use in patients with FAP at 400 mg twice a day (Steinbach et al., 2000). Furthermore, three large double blind randomized controlled trials, including the Adenoma Prevention with Celecoxib (APC) trial (Solomon et al., 2005), the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial (Arber et al., 2006), and the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial (Bresalier et al., 2005), were performed. All three trials showed that COXIBs prevent recurrence of sporadic adenomas with an increased cardiovascular risk. In the trials with celecoxib, a 2.5- to 3-fold increased relative risk for cardiovascular thromboembolic events was observed with a 400 mg twice-daily dosing celecoxib schedule compared with placebo, whereas a once-daily dosing schedule or 200 mg twice-daily dosing demonstrated much less risk rate compared with placebo (Solomon et al., 2006), indicating a trend for a dose-related increase in cardiovascular events. However, the detailed analysis of the APC trial found that a history of atherosclerotic heart disease was the only specific risk factor associated significantly with celecoxib to adverse cardiovascular events (Bertagnolli et al., 2009). Furthermore, a recent pooled analysis of adjudicated data from 6 placebo-controlled trials further demonstrated that the celecoxib-related cardiovascular risk is positively correlated with the drug dose and the baseline cardiovascular risk (pretreatment cardiovascular status) in patients (Solomon et al., 2008). More intriguingly, a recent report that retrieved all existing epidemiologic studies (case control and cohort studies) from 1980 shows that regular intake of NSAIDs significantly reduced the risk for CRC, breast, lung, and prostate cancer (Harris, 2009). The most important finding form this report is that the meta-analysis of independent estimates from 72 studies provides no evidence that daily use of the celecoxib increases the relative risk of cardiovascular disease. Another cohort study examined cardiovascular outcomes in approximately 1.4 million patients receiving NSAIDs or COXIBs showed that there was, again, no risk observed with celecoxib (Graham et al., 2005). Therefore, it is necessary to further assess the relative risks and benefits of celecoxib in different clinical settings such as people with or without vascular disease and patients with adenomas. Since all drugs are associated with some risk, any therapy has to weigh the potential risk against the potential benefit.

Another approach for decreasing the undesired side effects of COXIBs is to lower the drug dose used. The combinational treatment of NSAIDs with different agents that target key signaling pathways involved in cancer progression have been evaluated. It has been demonstrated that a EGFR signaling pathway is involved in many different types of cancer, including colorectal, breast, and lung cancer (Kelloff et al., 1996). EGFR activity has been associated with adenoma growth in $Apc^{Min/+}$ mice (Moran et al., 2004) and disruption of EGFR signaling through either kinase inhibition or genetic mutation inhibits polyp formation as well as the growth of established tumors (Roberts et al., 2002). Recent evidence showed that combined treatment with celecoxib and erlotinib (an EGFR tyrosine kinase inhibitor) had more effective prevention of polyp formation in $Apc^{Min/+}$ mice and more significant inhibition of tumor growth in a xenograft model than either drug individually (Buchanan et al., 2007). Moreover, a phase I clinical trial was recently completed to evaluate the optimal biological dose of celecoxib in combination with erlotinib in patients with advanced non–small cell lung cancer (Reckamp et al., 2006). This trial showed that there were no dose-limiting toxicities and no cardiovascular toxicities related to celecoxib at the dosing ranges of 200 mg to 800 mg twice daily. Another phase I trial showed that combination of bortezomib (an inhibitor of ubiquitin-proteasome pathway) and celecoxib at the dosing ranges of 200 mg to 400 mg twice daily was well tolerated in patients with advanced solid tumors (Hayslip et al., 2007). Similarly, a 5-lipoxygenase (5-LOX) inhibitor overcame a resistance of tumor cell to a SC-236 (a COXIB) and restore the ability of SC-236 to inhibit tumor growth in an animal model of breast cancer (Barry et al., 2009). A combinational treatment of celecoxib and a PPARγ agonist was significantly more effective than either alone in a mouse model of spontaneous breast cancer (Anderson et al., 2009). In addition, combination therapy with aromatase inhibitors (AIs) and celecoxib has better efficacy and safety for the treatment of patients with metastatic breast cancer than monotherapy (Falandry et al., 2009). Finally, pilot phase II studies in patients with metastatic breast cancer and advanced pancreatic carcinoma showed interesting findings that celecoxib enhances clinic benefit rate with decreasing certain chemotherapy-related toxic effects and is well tolerated without excess cardiotoxicity at a dose of 400–800 mg/day for a limited period of time (Fabi et al., 2008; Ferrari et al., 2006; Milella et al., 2004). These studies supports the notion that combinations of different agents for cancer prevention and treatment may be more effective than single agent therapy alone with minimal side affects.

COX-2 Regulation

To date COX-2 represents an important molecular target in CRC prevention and treatment. COX-2 is an immediate-early response gene normally absent from most cells but is induced mainly at sites of inflammation in response to inflammatory stimuli including pro-inflammatory cytokines such as IL-1α/β, IFN-γ, and TNF-α produced by inflammatory cells as well as tumor promoters such as tetradecanoyl phorbol acetate (TPA) and Ras (Dubois *et al*., 1998; Wang *et al*., 2005). By contrast, COX-1 generally contributes to maintenance of the gastric mucosa, regulation of renal blood flow in the afferent vessels of the kidney, and regulation of platelet aggregation.

COX-2 expression is regulated in both transcriptional and post-transcriptional levels. It is well established that the COX-2 transcription can be regulated by various transcription factors such as NF-κB, C/EBP, CREB, NFAT, AP-1, and PPAR. COX-2 mRNA is also modulated by post-transcriptional mechanism via AU-rich regions in its 3′-untranslated region (3′UTR). The RNA-binding proteins Hu antigen R (HuR) and tristetraprolin (TTP) bind AU-rich elements in the 3' UTR of COX-2 to stabilize or to decay its mRNA, respectively (Young et al., 2009). Recently, MicroRNAs (miRNAs) have been suggested to silence COX-2 expression by translational repression and/or degradation of its mRNA via 3' UTR (Daikoku et al., 2008; Strillacci et al., 2009). In addition to the inflammatory

microenvironment, a hypoxic environment also induces COX-2 expression in colorectal tumor cells via HIF-1α factor (Kaidi et al., 2006). In contrast, a 2-arachidonoyl-glycerol (an endocannabinoid) is able to suppress elevation of COX-2 expression in response to proinflammatory and excitotoxic stimuli in neurons and astroglial cells (Zhang and Chen, 2008). Caveolin-1 is a scaffold protein that has been proposed to function as a tumor suppressor in human cancer cells. Caveolin-1 downregulated COX-2 mRNA and protein levels as well as the production of PGE_2 and cell proliferation in human CRC cell lines (Rodriguez et al., 2009).

COX-2 and IBD

The pro-inflammatory enzyme, COX-2, is induced in large intestinal epithelium in active human IBD and in inflamed tissues of IL-10 deficient mice (a mouse model of IBD) (Shattuck-Brandt et al., 2000; Singer et al., 1998). Since both nonselective NSAIDs and COXIBs can be used to treat arthritis and reduce the risk of developing CRC, these agents might be expected to have a chemopreventive role in IBD and IBD-associated CRC. Although the 5-aminosalicylate-based compounds have remained in the mainstream for the treatment of IBD patients, evidence from clinical studies has shown conflicting data in treatment of IBD with other non-selective NSAIDs or COXIBs. In general, COXIBs have fewer gastrointestinal side effects than the non-selective NSAIDs (Felder et al., 2000; Mahadevan et al., 2002). A recent double-blind and placebo-control study showed that etoricoxib (COXIB) therapy is safe and beneficial in most IBD patients without exacerbation of IBD- and GI-related complications (El Miedany et al., 2006). Similar to the results from clinic studies, the conflicting results have emerged regarding the effects of NSAIDs on IBD in animal models (Wang et al., 2005). Genetic evidence showed that COX-2 deficient mice have increased sensitivity to chemically-induced colitis (Morteau et al., 2000). However, the recent observation that combinational treatment of a COXIB and an inhibitor of nitric oxide synthase (iNOS) has maximal protective effect on chemically-induced colitis supports the idea that simultaneous inhibition of iNOS and COX-2 might have some potential in the treatment of colitis (Dudhgaonkar et al., 2007). Further clinical studies are required for evaluating the relative risks and benefits of COXIBs in patients with IBD.

Despite epidemiological and experimental evidence strongly implicating chronic inflammation as a risk factor for CRC, surprisingly little research has directly addressed the question of how chronic inflammation results in neoplastic transformation and progression. It is generally thought that chronic inflammatory orchestrates a tumor-supporting microenvironment that promotes tumor initiation, progression, angiogenesis, and metastasis. In a large case-control study, there was a trend for long-term NSAID consumption in protecting against CRC in patients with IBD (Bernstein et al., 2002; Eaden, 2003). In a mouse model for colitis-related carcinogenesis, dietary administration of a nimesulide (COXIB) effectively suppressed the development of colonic tumor induced by AOM/DSS (Kohno et al., 2005). These findings support the hypothesis that COX-2 might play a role in IBD-associated CRC.

COX-2 and CRC

The first evidence linking COX-2 to carcinogenesis emerged from studies on CRC (Eberhart et al., 1994). Direct molecular evidence that COX-2 plays a key role in colorectal carcinogenesis was obtained from studies in animal models. Genetic studies demonstrate that deletion of the COX-2 gene results in decreased tumor formation in both the small intestine and colon of $Apc^{Min/+}$ mice (a mouse model of CRC) (Chulada et al., 2000) as well as in $Apc^{\Delta 716}$ mice, another *Apc* mutant model (Oshima et al., 1996). Transgenic mice with

COX-2 overexpression in the colon did not develop tumors spontaneously, but did have a higher tumor load compared to wild-type mice following azoxymethane (AOM) treatment (Al-Salihi et al., 2009). Similar observations were found in skin and gastric cancers (Leung et al., 2008; Muller-Decker et al., 2002). Although the data that overexpression of COX-2 initiates colorectal carcinogenesis in transgenic mouse models have not been reported, overexpression of COX-2 in transgenic mice using a murine mammary tumor virus (MMTV) promoter induced breast carcinomas formation (Liu et al., 2001). Moreover, COX-2 transgenic mice driven by a bovine keratin promoter spontaneously developed pancreatic ductal adenocarcinomas whereas treatment of these mice with celecoxib completely inhibited the tumor formation (Colby et al., 2008). These results are consistent with human clinical and epidemiologic data.

Although the focus of clinical cancer research with NSAIDs was initially on chemoprevention, the potential therapeutic use of NSAIDs in cancer also obtained considerable attention. Since chemotherapeutic agents and radiation therapy enhance COX-2 protein expression in human cancer cells, which in turn results in resistance to therapy, it would be important to determine whether COXIBs enhance the chemosensitivity and radiosensitivity of tumor cells. Preclinical studies showed that celecoxib potentiated the effects of radiotherapy (Davis et al., 2004) and a combination treatment of celecoxib with oxalipatin had synergistic effects on inhibition of tumor growth in a mouse xenograft model of human colon cancer (Zhao *et al*., 2009). More interestingly, combined treatment with S1 (a oral fluoropyryzine drug) and a COXIB more effectively restrained liver metastasis of CRC cells than either alone in a nude mouse model of liver metastasis (Tachimori et al., 2008). A phase II study of celecoxib with cisplatin plus etoposide in extensive-stage small cell lung cancer were performed and showed promising results, although the study were stopped earlier because the safety concerns regarding celecoxib (Aruajo et al., 2009).

COX-2 Pathways

The COX enzymes convert free arachidonic acid (AA) into prostanoids, including prostaglandins (PGs) and thromboxanes (TXs). The key regulatory step in this process is the enzymatic conversion of the AA to PGG_2, which is then reduced to an unstable endoperoxide intermediate, PGH_2. PGH_2 is sequentially metabolized to five active, structurally related prostanoids, including PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (TxA_2), in a cell type-specific manner via specific PG synthases. These bioactive lipids exert their cellular functions by binding cell surface receptors that belong to the family of seven transmembrane G-protein-coupled rhodopsin-type receptors. These receptors are designated DP for the PGD_2 receptor, EP (EP1, EP2, EP3, and EP4) for PGE_2 receptors, FP for the $PGF_{2\alpha}$ receptor, IP for the PGI_2 receptor, and TP for the TXA_2 receptor. Moreover, some PGs can also bind to nuclear receptors such as peroxisome proliferators-activated receptors (PPARs). It has been shown that the PGD_2 dehydration product 15-deoxy-$^{\Delta 12,\Delta 14}PGJ_2$ ($15dPGJ_2$) is a natural ligand for the PPARγ receptor (Forman et al., 1995; Kliewer et al., 1995), while PGI_2 activates PPARδ by directly binding to it (Forman et al., 1997; Gupta et al., 2000). Additionally, PGE_2 has been shown to indirectly transactivate PPARδ (Wang et al., 2004). Recent studies suggest that PPARγ and PPARδ play an important role in modulating colorectal carcinogenesis as well as other types of cancer (Panigrahy et al., 2005; Wang and Dubois, 2008; Wang et al., 2006b; Yin et al., 2005; Zuo et al., 2009).

In addition to conversion of free arachidonic acid into prostanoids, COX-2 is also able to metabolize endocannabinoids, 2-arachidonylglycerol (2-AG) and anandamide (AEA), into prostaglandin glycerol esters (PG-G) and ethanolamides (PG-EA), respectively (Kozak et al., 2002). These COX-2-derived metabolites of endocannabinoids no longer bind to cannabinoid receptors but do represent a new class of biologically active eicosanoids that

modulate cellular functions such as regulation of IL-2 in T cells (Rockwell et al., 2008). Furthermore, COX-2 is required for endocannabinoid-induced cell apoptosis in CRC cell lines and keratinocytes (Patsos *et al*., 2005; Van Dross, 2009).

PGE_2 Mediates the Effects of COX-2 on IBD and CRC

COX-2 derived PGs are involved in a variety of pathologic processes, including IBD and CRC. A great effort has been made to identify which of the individual PGs are directly involved in IBD and CRC. Multiple lines of evidence have demonstrated that PGE_2 mediates the pro-inflammatory and tumor-promoting effects of COX-2 in IBD and CRC. The steady-state cellular levels of PGE_2 depend on the relative rates of COX-2/PGE synthase-dependent biosynthesis and 15-hydroxyprostaglandin dehydrogenase (15-PGDH)-dependent degradation.

Recent research has determined that PGE_2 is a key mediator of IBD (Gould et al., 1981; MacDermott, 1994; Sheibanie et al., 2007). In an experimental model for IBD, PGE_2 appears to have a dual effect. High levels of PGE_2 exacerbate the inflammatory process (Sheibanie et al., 2007). On the other hand, PGE_2 signaling is required for suppressing colitis symptoms and protecting mucosal damage by maintaining the integrity of the epithelial intestinal wall, presumably through the enhancement of epithelial survival and regeneration (Jiang et al., 2007). Moreover, a genetic study reveals that only EP4-deficient mice are more sensitive to DSS treatment and developed severe colitis but mice deficient in EP1, EP2, EP3, DP, FP, IP, or TP are not sensitive to DSS treatment, respectively (Kabashima et al., 2002). Further studies are necessary to define the role of PGE_2 and it's receptors in IBD.

Pro-inflammatory PGE_2 plays a predominant role in promoting colorectal tumor growth. PGE_2 is the most abundant PG found in human CRC (Rigas et al., 1993). In contrast, 15-PGDH is highly expressed in normal colon mucosa but is ubiquitously lost in most human colorectal cancers (Backlund et al., 2005). PGE_2 protects small intestinal adenomas from NSAID-induced regression in $Apc^{Min/+}$ mice (Hansen-Petrik et al., 2002) whereas loss of 15-PGDH leads to resistance to anti-tumor effects of celecoxib in AOM mouse model (Yan *et al*., 2009). Recent studies showed that PGE_2 treatment dramatically increased both small and large intestinal adenoma burden in $Apc^{Min/+}$ mice and significantly enhanced AOM-induced colon tumor incidence and multiplicity (Kawamori et al., 2003; Wang et al., 2004). Furthermore, elevated endogenous PGE_2 via loss of 15-PGDH promoted colon tumor growth in $Apc^{Min/+}$ and AOM mouse models (Myung et al., 2006). In contrast, inhibition of endogenous PGE_2 via genetic deletion of mPGES-1 suppressed intestinal tumorigenesis in $Apc^{Min/+}$ and AOM models (Nakanishi et al., 2008). The central role of PGE_2 in colorectal tumorigenesis has been further confirmed by evaluating mice with homozygous deletion of PGE_2 receptors (Mutoh et al., 2002; Sonoshita et al., 2001; Watanabe et al., 1999).

To understand mechanism(s) underlying effects of PGE_2 on cancer progression, researchers have been investigating precisely how PGE_2 promotes tumor growth and its signaling pathways. Several reports have shown that PGE_2 promotes colorectal tumor growth by stimulating angiogenesis, cell invasion, cell growth and survival (Wang and Dubois, 2006). These essential cellular processes are regulated by PGE_2 activated signaling pathways, including EGFR-PI3K-Akt, Ras-MAPK, PPARδ, VEGF, Bcl-2, chemokines and their receptors (Wang and Dubois, 2006; Wang et al., 2006a). PGE_2 also activates canonical Wnt signaling by activating Tcf-4 transcription factors via stabilizing β-catenin in CRC cells (Castellone et al., 2005). Conversely, many of the downstream pathways of PGE_2 also upregulates COX-2 expression. Such feedback loops may amplify the activity of the COX-2 pathway and may magnify the potency of COX-2 inhibitors.

Conclusions

To date prolonged use of high doses of NSAIDs (except for aspirin) is not recommended because of unacceptable cardiovascular side effects. However, recent studies show that celecoxib may be safe for preventing CRC formation and development in certain people. Further investigation will be required to assess the balance of the relative risks and benefits in different clinical settings such as patients with FAP. The mechanism of the side effects of NSAIDs is unclear. A potential explanation is that the side effects are associated with a global reduction in PG production. This hypothesis is supported by a observation that COX-2 deficiency contributes to the pro-atherogenic properties of HDL with increased lipid deposition in the aorta and the dramatic imbalance in circulating prostanoids, such as decreased serum PGI_2 coupled with increased PGE_2 and TXB_2 in mice (Narasimha et al., 2007). Therefore, it will be important to develop chemopreventive agents that do not inhibit production of other prostanoids, such as the anti-thrombotic PGI_2. Given that PGE_2 appears to be the main pro-carcinogenic eicosanoid, more selective pharmacological inhibition of PGE_2 production downstream of COX-2 may be superior and result in fewer side effects. Thus, it is now crucial to evaluate whether PGE_2 receptor antagonists and inhibitors of PGE_2 synthases have better specificity for the prevention of CRC and result in minimal adverse effects. Of course, another option may be to modulate the expression levels of 15-PGDH.

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