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Pro-inflammatory prostaglandins and progression of colorectal cancer

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Abstract

Chronic inflammation is a risk factor for several gastrointestinal malignancies, including esophageal, gastric, hepatic, pancreatic and colorectal cancer. It has long been known that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) reduces the relative risk of developing colorectal cancer. NSAIDs exert their anti-inflammatory and anti-tumor effects primarily by inhibiting activity of cyclooxygenase (COX) enzymes. Cyclooxygenase enzymes catalyze the conversion of arachidonic acid into prostanoids, including prostaglandins (PGs) and thromboxanes (TXs). Emerging evidence demonstrates that prostaglandins play an important role in inflammation and cancer. In this review, we highlight recent breakthroughs in our understanding of the roles of the different prostaglandins in colorectal cancer (CRC) and inflammatory bowel disease (IBD). These findings may provide a rationale for the development of new anti-inflammatory therapeutic approaches to cancer prevention and/or treatment.

Keywords

cyclooxygenase; prostaglandins; NSAIDs; inflammation; colorectal cancer

Introduction

Clinical and epidemiologic studies suggest that chronic inflammation caused by infectious or autoimmune diseases is clearly associated with increased risk of cancer, including colorectal cancer (CRC) [1] and chronic inflammation contributes to the development of approximately 15–20% of malignancies worldwide [2]. Experimental studies indicate that inflammation promotes tumor growth, in part, through stimulation of proliferation and angiogenesis as well as inhibition of apoptosis and immune surveillance. The best evidence for the link between inflammation and tumor progression come from recent epidemiologic studies and clinical trials showing that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) reduced the relative risk of developing colorectal cancer by 40–50% [3]. NSAIDs are thought to exert their anti-inflammatory, analgesic and anti-pyretic effects mainly by targeting cyclooxygenase (COX) enzymes [4]. The COX enzyme exists in three isoforms commonly referred to as COX-1, COX-2, and COX-3. COX-1 is constitutively expressed in a broad range of cells and

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tissues and its expression remains constant under most physiological or pathological conditions. COX-1 contributes to maintenance of the gastric mucosa, regulation of renal blood flow in the afferent vessels of the kidney, and regulation of platelet aggregation. By contrast, 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 [5]. COX-2 is involved in inflammation and tumorigenesis. COX-3 is an acetaminophen-sensitive splice variant of COX-1 and its function remains unknown. Therefore, COX-2 is a pro-inflammatory mediator and NSAIDs and specific COX-2 inhibitors are currently used to treat acute pain as well as the signs and symptoms of osteoarthritis and rheumatoid arthritis [6].

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 while maintaining 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. An abnormal mucosal immune response is thought to result in chronic inflammation such as arthritis and inflammatory bowel disease (IBD). IBD in humans is a complex class of disorders that has been grouped into two major forms, ulcerative colitis (UC) and Crohn's disease (CD). These chronic conditions of the gut ordinarily affect individuals between the age of 16 and 40 and can cause significant morbidity. Chronic IBD (especially pan-colitis) significantly increases the risk of developing colorectal cancer [7]. IBD is thought to result from inappropriate activation of immune responses and/or a deficient feedback system that normally down-regulates the mucosal response to luminal factors.

The first evidence linking COX-2 to carcinogenesis emerged from studies on CRC [8]. Several subsequent reports confirmed that elevated COX-2 expression was found in approximately 50% of adenomas and 85% of adenocarcinomas [9,10]. Similarly, 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) [11,12]. An increasingly large body of evidence from population-based studies and clinical trials have shown that regular use of NSAIDs, including aspirin and related drugs, over a 10–15 year period reduces the relative risk of developing colorectal cancer and adenomas by 40–50% [3]. In particularly, aspirin specifically prevents the subgroup of colon cancers in which COX-2 is most highly induced [13]. Furthermore, NSAID use leads to the regression of preexisting adenomas in patients with the hereditary colon cancer syndrome, familial adenomatous polyposis coli (FAP) [14,15]. 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 COX-2 gene results in decreased tumor formation in both the small intestine and colon of Apc^{Min} mice (a mouse model of CRC) [16] as well as in $Apc^{\Delta 716}$ mice, another Apc mutant model [17]. Although the effects of COX-2 overexpression upon 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 [18]. Moreover, transgenic mice with COX-2 expression driven by the keratin-5 promoter did not develop skin cancer spontaneously, but were much more sensitive to carcinogen-induced tumor formation [19].

The COX enzymes convert free arachidonic acid into prostanoids, including prostaglandins (PGs) and thromboxanes (TXs). The key regulatory step in this process is the enzymatic conversion of arachidonate to PGG_2, which is then reduced to an unstable endoperoxide intermediate, PGH_2. Specific PG synthases in turn metabolize PGH_2 to at least five structurally related bioactive lipid molecules, including PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (TxA_2), in a cell type-specific manner. PGs are unstable compounds that are rapidly

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metabolized *in vivo* [20]. PGE_2 and $PGF_{2\langle}$ are rapidly metabolized to a stable 13,14-dihydro-15-keto-PGA_2 (PGEM) and 13,14-dihydro-15-keto-$PGF_{2\langle}$ *in vivo* by the enzyme 15-hydroxy prostaglandin dehydrogenase (15-PGDH), respectively. PGI_2 is non-enzymatically hydrated to 6-keto $PGF_{1\langle}$, and then quickly converted to the major urinary metabolite, 2,3-dinor-6-keto $PGF_{1\langle}$ and PGD_2 is also rapidly metabolized to 15-deoxy-$^{\Delta 12}$, $^{\Delta 14}PGJ_2$ ($15dPGJ_2$) and 11β-$PGF_{2\langle}$ *in vivo*. Moreover, TXA_2 is rapidly hydrolyzed to TXB_2 in a non-enzymatic manner. Prostaglandins exert their cellular functions by binding cell surface receptors that belong to the family of seven transmembrane G protein-coupled rhodopsin-type receptors. These cell surface receptors are designated DP for the PGD_2 receptor, EP (EP1, EP2, EP3, and EP4) for the PGE_2 receptors, FP for the $PGF_{2\alpha}$ receptor, IP for the PGI_2 receptor, and TP for the TxA_2 receptor. In some cases, however, certain prostaglandins and their metabolites bind nuclear receptors such as peroxisome proliferator-activated receptors (PPARs). It has been shown that PGI_2 can transactivate PPARδ [21], while $15dPGJ_2$ is a natural ligand for PPARγ [22]. Moreover, recent studies show that PGE_2 indirectly induces PPARδ activation in certain contexts [23].

Prostaglandins and colorectal cancer

The prostanoids are involved in a variety of pathophysiologic processes, including modulation of the inflammatory reaction, gastrointestinal cytoprotection and ulceration, angiogenesis, cancer, hemostasis and thrombosis, renal hemodynamics, and progression of kidney disease. Multiple lines of evidence demonstrate that overexpression of COX-2 in epithelial, mesenchymal, and inflammatory cells leads to the production of multiple PGs, which in turn promote angiogenesis, protect against apoptosis, stimulate proliferation, induce metastasis, and suppress cell-mediated immune responses. A great effort has been made to identify which of the individual PGs are directly involved in CRC. A large body of evidence has demonstrated that PGE_2 mediates the tumor-promoting effects of COX-2 in colorectal cancer. Less evidence supports a role for other prostaglandins in CRC.

PGE_2

Recent research has indicated that PGE_2 is a key mediator of acute inflammatory responses [24], stem cell differentiation [25], arthritis [26], and inflammatory bowel disease (IBD) [27]. Direct evidence came from observations that blocking either PGE_2 synthases or PGE_2 receptors impaired both acute and chronic inflammatory responses. Mice deficient in PGE_2 synthase displayed a marked reduction in acute pain during the inflammatory response and collagen antibody-induced arthritis (an animal model of rheumatoid arthritis) [28]. EP1 receptor-deficient mice exhibited a reduction of their pain-sensitivity responses in two acute prostaglandin-dependent models [29]. Moreover, EP4 receptor-deficient mice showed decreased incidence and severity of collagen antibody-induced arthritis [30] with a possible contribution of EP_2 [31]. These studies support the notion that PGE_2 mediates the effects of COX-2 during acute pain and arthritis. In an experimental model for IBD, PGE_2 appears to have a dual effect. High levels of PGE_2 exacerbate the inflammatory process [27]. On the other hand, PGE_2 signaling suppresses colitis symptoms and mucosal damage by protecting the integrity of the epithelial intestinal wall, presumably through the enhancement of epithelial survival and regeneration [32]. Moreover, a genetic study reveals that only EP4-deficient mice and not mice deficient in either EP1, EP2, EP3, DP, FP, IP, or TP are more sensitive to DSS treatment and developed severe colitis [33]. Further studies are necessary to define the role of PGE_2 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 colorectal cancer tissues [34]. The steady-state cellular levels of PGE_2 depend on the relative rates of COX-2/PGE synthase-dependent

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biosynthesis and 15-hydroxyprostaglandin dehydrogenase (15-PGDH)-dependent degradation. 15-PGDH is highly expressed in normal colon mucosa but is ubiquitously lost in most human colorectal cancers [35]. A recent study showed that PGE_2 treatment dramatically increased both small and large intestinal adenoma burden in $Apc^{Min/+}$ mice and significantly enhanced colon carcinogen azoxymethane (AOM)-induced colon tumor incidence and multiplicity [23,36]. Furthermore, elevated endogenous PGE_2 via loss of 15-PGDH promoted colon tumor growth in $Apc^{Min/+}$ and AOM mouse models [37]. Similarly, increased endogenous PGE_2 by overexpressing both COX-2 and microsomal prostaglandin E synthase-1 in the stomach is sufficient to induce gastric tumor formation [38]. PGE_2 also protects small intestinal adenomas from NSAID-induced regression in $Apc^{Min/+}$ mice [39]. The central role of PGE_2 in colorectal tumorigenesis has been further confirmed by evaluating mice with homozygous deletion of PGE_2 receptors [40–42].

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 inhibiting apoptosis [43]. 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 [43, 44]. PGE_2 also activates canonical Wnt signaling by activating Tcf-4 transcription factors via stabilizing β-catenin in CRC cells [45]. 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.

TxA_2

Although the role of TxA_2 in atherogenesis has been established [46], few studies have delineated the biological function of TxA_2 in CRC and IBD. TxA_2 is the only other COX-2 derived prostaglandins implicated in oncogenesis. TxA_2 has been shown to promote tumor growth and tumor-associated angiogenesis [47]. Moreover, it has been reported that TxA_2 synthase inhibitor blocks colorectal carcinoma liver metastasis in an *in vivo* study [48]. However, disruption of TP receptor doesn't affect colon tumor formation in AOM-treated mice [41]. Additional research is needed to determine the role of TxA_2 signaling in CRC. In an animal model of IBD, conflicting results have emerged regarding the role of TxA_2-TP system in IBD. Treatment of a TP antagonist significantly reduced the colonic damage [49], while deletion of TP didn't affect colitis formation caused by DSS [33]. These conflicting data dictate the need of additional research to address the role of TxA_2 in CRC and IBD.

PGD_2

Although PGD_2 have been implicated as an anti-inflammatory regulator of the IBD [50], the role of PGD_2 in colon cancer is not defined. PGD_2 and/or its metabolites may have tumor inhibitory effects. Recent study shows that disruption of the gene for hematopoietic PGD synthase in $Apc^{Min/+}$ mice accelerates intestinal tumor growth, while $Apc^{Min/+}$ mice with transgenic human hematopoietic PGD synthase exhibit fewer intestinal adenomas than controls [51]. These results suggest that PGD_2 serves as tumor suppressor in colorectal cancer. However, the evidence from DP receptor studies in CRC mouse models don't support the hypothesis that PGD_2 has tumor inhibitory effects. For example, disruption of the DP receptor didn't affect colon tumor formation in AOM-treated mice [41]. Treatment with a selective DP antagonist significantly reduced susceptibility of post-colitis rats to the development of aberrant crypt foci [52]. One possible explanation for the differences in phenotype caused by PGD synthase versus DP in mouse models may be due to a fact that PGD_2 exerts its biological functions through either DP or/and PPARγ receptor. It is possible that the anti-tumor effect of

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PGD_2 is mediated by PPARγ since PGD_2 can be metabolized to $15dPGJ_2$, which is a endogenous ligand for the PPARγ. Activation of PPARγ results in growth arrest of colon carcinoma cells through induction of cell differentiation and inhibition of cell proliferation or induction of apoptosis. Alternatively, overexpression of PGD synthase may shift the conversion of PGH_2 away from PGE_2, which in turn suppresses tumor growth.

$PGF_{2\alpha}$

Although the emerging data support the role of $PGF_{2\alpha}$ in acute and chronic inflammation [53], However, one study showed that FP is not involved in the progression of chronic inflammation in IBD [33]. Furthermore, there are no clear studies showing that $PGF_{2\alpha}$ participates in IBD. Similarly, the observation that $PGF_{2\alpha}$ failed to induce cell proliferation in CRC cell lines and deletion of FP receptor didn't affect colon tumor formation in AOM-treated mice suggests that $PGF_{2\alpha}$ is not involved in colorectal cancer progression [41,54].

PGI_2

In normal physiological processes, COX-1-derived PGI_2 is a major prostaglandin product in the gastrointestinal tract and plays a role in the cytoprotection of gastric mucosal surfaces and in maintaining normal vasculature [55]. Under pathological conditions, PGI_2 serves as a mediator of acute and chronic inflammation. Loss or inhibition of IP (the prostacyclin receptor) reduces pain and inflammation in a chronic model of inflammatory arthritis [56]. In an animal model of IBD, another study showed that IP is not involved in chronic inflammation [33]. There is also no other report showing that PGI_2 is implicated in IBD. Although one study showed that the IP receptor is not involved in colon tumor formation in AOM-treated mice [41], little is known about the role of PGI_2 and IP in CRC. Since PGI_2 can activate PPARδ in CRC cells [21] and activation of PPARδ accelerates intestinal tumor growth in $Apc^{Min/+}$ mice [57], it is conceivable that PGI_2 may participate in the colon tumor progression through PPARδ. Further work is necessary to explore the role of PGI_2 and IP in colon carcinogenesis.

Conclusions

Prolonged use of high doses of NSAIDs (except for aspirin) is associated with unacceptable cardiovascular side effects [58–60]. The mechanism of the side effects of NSAIDs is unclear. A potential explanation for the cardiovascular side effects of NSAIDs is proposed based on the following observations. The synthesis of PGI_2 depends principally on COX-2 activity in the vascular wall, whereas the production of TxA_2 in platelets is dependent on COX-1. Since PGI_2 antagonizes the biological functions of TxA_2 produced by platelets, inhibition of PGI_2 may shift the homeostatic balance toward more the pro-thrombotic TxA_2 effects. The potential inhibition of endothelial cell–derived COX-2 activity and subsequent PGI_2 production by COX-2 selective inhibitors may promote platelet aggregation and lead to increased the risk of coronary thrombosis and stroke [61]. In addition, PGI_2 appears to serve an important role in protecting cardiomyocytes from oxidant stress, which is a key risk factor for atherogenesis [62]. 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 colon cancer and result in minimal adverse effects. Of course, another option may be to modulate the expression levels of 15-PGDH in order to decrease the levels of PGE_2 in the tumor microenvironment.

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