PPARδ and PGE₂ signaling pathways communicate and connect inflammation to colorectal cancer

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The nuclear hormone receptor peroxisome proliferator-activated receptor δ (PPARδ) is a ligand-dependent transcription factor that is involved in fatty acid metabolism, obesity, wound healing, inflammation, and cancer. Despite decades of research, the role of PPARδ in inflammation and colorectal cancer remains unclear and somewhat controversial. Our recent work presented the first genetic evidence demonstrating that PPARδ is required for chronic colonic inflammation and colitis-associated carcinogenesis. We also found that a PPARδ downstream pathway, namely the COX-2-derived PGE₂ signaling, mediated crosstalk between tumor epithelial cells and macrophages to promote chronic inflammation and colitis-associated tumor genesis. In this brief review, we summarize recent studies on the role of PPARδ in inflammatory bowel disease (IBD) and colorectal cancer (CRC) and highlight recent advances in our understanding of how PPARδ and COX-2-derived PGE₂ signaling coordinately promote chronic colonic inflammation and colitis-associated tumorigenesis. Elucidating the role of PPARδ in inflammation and CRC may provide a rationale for development of PPARδ antagonists as new therapeutic agents in treatment of IBD and CRC.

Keywords: Colorectal cancer; inflammation; colitis-associated tumorigenesis; peroxisome proliferator-activated receptor; chemokines; and COX-2-driven PGE₂

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Colorectal cancer (CRC) is the third most common solid malignancy and the second leading cause of cancer deaths in the USA. CRC includes at least three major forms: hereditary, sporadic, and colitis-associated CRC. A large body of evidence reveals that genetic mutations, epigenetic changes, chronic inflammation, diet, and lifestyle are risk factors for developing CRC. Indeed, ulcerative colitis, the most common form of inflammatory bowel disease (IBD), is associated with an increased risk for the development of CRC [¹]. The best evidence for the link between chronic inflammation and CRC came from epidemiologic studies and clinical trials showing that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) reduced the relative risk of developing CRC by 40-50% [²]. In
particular, daily use of aspirin significantly suppressed adenoma growth in patients with familial adenomatous polyposis (FAP) [3] and cancer incidence in patients with HNPCC [4]. FAP is due to a germ-line mutation in one allele of the tumor suppressor gene adenomatous polyposis coli (APC). In sporadic CRC, the data from clinical trials have revealed that daily use of aspirin prevented adenoma recurrence in patients with a history of colorectal adenomas [5-8]. Moreover, the epidemiologic and clinical evidence showing that daily use of aspirin prevented metastatic spread [9] and inhibited the spread of primary tumor cells to other organs of the body after the diagnosis of localized disease, in particular CRC [10], suggests the potential therapeutic efficacy of NSAIDs in advanced CRC. Epidemiologic studies further showed that regular use of aspirin specifically reduced risk of the subgroup patients whose colon tumors expressed cyclooxygenase 2 (COX-2) at higher levels [11] and its use after the diagnosis of CRC at stage I, II and III prolonged overall survival in patients whose tumors overexpress COX-2 [12]. These findings suggest that the preventive and inhibitory effects of aspirin on CRC might depend on the presence of COX-2.

COX-2 is an immediate-early response gene that is normally absent from most cells but is highly induced at sites of inflammation and in the tumor microenvironment [13]. A large body of evidence reveals that COX-2 expression is elevated in up to 90% of colorectal carcinomas and 50% of adenomas [14] and its expression is correlated with a lower survival rate among CRC patients [15]. Our group and others have demonstrated that COX-2 plays important roles in inflammation and cancer [16]. COX enzymes convert arachidonic acid into an endoperoxide intermediate that can be further metabolized to five structurally related prostanoids, including prostaglandins (PGs). Thus, the biological functions of COX enzymes depend on which COX-derived prostanoids are produced in cancers. PGE_2 is the most abundant PG found in human CRC and plays a predominant role in promoting tumor growth [17,18]. Emerging epidemiologic evidence and a phase II biomarker study showed that urinary PGE_2 metabolite (PGE-M) levels were associated with an increased risk of developing colorectal [19-21], gastric [22], and breast cancer [23,24] and that PGE-M levels correlated with disease progression in head and neck squamous cell carcinomas [25]. More importantly, epidemiologic studies revealed that levels of urinary PGE-M in healthy humans [26] and breast cancer patients [23,24] are suppressed significantly not only by treatment with nonselective NSAIDs, including aspirin, but also by COX-2 selective inhibitors, suggesting that the majority of PGE_2 formed in vivo may be derived from COX-2. Phase II studies also showed that non-small cell lung cancer (NSCLC) patients with complete and partial responses to adjuvant therapy with paclitaxel, carboplatin, and celecoxib experienced a significant decrease in the level of urinary PGE-M [27] and recurrent NSCLC patients with lower urinary PGE-M levels had a longer survival than those with no change or an increase in PGE-M when treated with celecoxib and docetaxel [28]. Collectively, these results indicate that the anti-tumor effects of NSAIDs, including aspirin, is likely due to reduction of PGE_2 levels by inhibiting COX-2 activity.

Our previous study showed that PGE_2 accelerated colonic adenoma formation and growth via activation of peroxisome proliferator-activated receptor δ (PPARδ) in ApcMin/+ mice [29]. The ApcMin/+ mouse carries a point mutation at one allele of the Apc gene, which is utilized as a model for FAP and a pre-malignant model for sporadic CRC in humans. We found that PGE_2 indirectly transactivated PPARδ via a PI3K-AKT signaling in tumor epithelial cells [29]. These results demonstrate that PPARδ is one of the downstream targets of PGE_2. This finding is likely to be clinically relevant because a case-control study in a large population showed that the protective effect of NSAIDs against colorectal adenomas was reported to be modulated by a polymorphism in the PPARδ gene [30]. PPARδ is a member of the nuclear hormone superfamily that is ligand-dependent transcription factors. This receptor has been implicated in a variety of physiology and pathologic processes, such as nutrient metabolism, energy homeostasis, inflammation, and cancer. However, the role of PPARδ in IBD and CRC remains unclear and somewhat controversial based on the results from PPARδ knockout mouse studies [31]. The conflicting results may be due to different deletion strategies used to knock out PPARδ. The deletion of Ppard exon 4 and/or 5, which encode an essential portion of the DNA binding domain, is believed to totally disrupt PPARδ function as a transcriptional factor. In contrast, the deletion of exon 8, the last exon of Ppard gene, is thought to generate a hypomorphic allele, which retains some aporeceptor function. All results from mice in which Ppard exons 4-5 or exon 4 were deleted suggest that PPARδ has pro-inflammatory and pro-tumor effects in mouse models of CRC [32,33]. In addition to CRC, a recent study showed that loss of PPARδ by deletion of its exons 4-5 also suppressed UV-induced skin tumor burden [34]. In contrast, all results from mice in which Ppard exon 8 was deleted indicate that PPARδ exerts anti-inflammatory and anti-tumor effects in mouse models of CRC and colitis-associated tumor genesis [35,36]. To further clarify the role of PPARδ in colorectal tumorigenesis, another approach would be to study the impact of PPARδ overexpression on tumorigenesis because the levels of PPARδ have been reported to be elevated in human colorectal adenomas and carcinomas [37-40]. Shureiqi’s group recently reported that targeted intestinal PPARδ overexpression promoted colonic tumorigenesis in...
azoxymethane (AOM)-treated PPARδ transgenic mice [41]. AOM is a potent carcinogen used to induce colorectal cancer in mice and rats. Similarly, targeted mammary epithelium PPARδ overexpression accelerated estrogen receptor-positive mammary neoplasia in PPARδ transgenic mice [42]. In addition, a recent case-control study showed that genetic variants (SNPs) of Ppard gene were associated with increased risk of gastric cancer [43]. Collectively, these recent findings support the hypothesis that PPARδ promotes colorectal tumorigenesis.

In order to investigate mechanisms involved in colitis-associated carcinogenesis, investigators have developed several animal models. In these models, there are at least two approaches used to induce colitis-associated carcinogenesis. One way is to induce chronic colonic inflammation by dextran sulfate sodium (DSS) in mice pretreated with AOM or in mice with a genetic predisposition to intestinal tumor formation such as the ApcMin/+ mouse. Another approach is to initiate colonic epithelial cell transformation by AOM in mice with a genetic predisposition to IBD such as the Il-10−/− mouse. Although repeated DSS treatment induces chronic colonic inflammation, the DSS model represents a process of injury and wound healing. A recent report indicated that deletion of PPARδ in intestinal epithelial cells did not affect tumor incidence in AOM/DSS-treated mice [44]. Our recent results revealed that loss of PPARδ by deletion of its exons 4-5 attenuated chronic colonic inflammation and colitis-associated adenoma formation and growth with a reduction of certain pro-inflammatory mediators, including chemokines/cytokines, COX-2, and PGE2 in both DSS-treated ApcMin/+ mice and AOM-treated Il-10−/− mice [45]. In this study, we also found that PPARδ activation induced COX-2 expression in colonic tumor epithelial cells. COX-2-derived PGE2 stimulates macrophages to produce pro-inflammatory chemokines that recruit pro-inflammatory leukocytes from the circulation to local inflammatory sites and cytokines that contribute to colitis-associated tumorigenesis. PGE2 has also been shown to promote tumor development by: 1) directly inducing tumor epithelial cell proliferation, survival, and migration/invasion and 2) impacting the tumor microenvironment so that it supports tumor progression by inhibiting immunosurveillance and inducing angiogenesis [17]. Our results suggest that PPARδ accelerates chronic colonic inflammation and inflammation-associated tumor growth via the COX-2-derived PGE2 signaling pathway. These results should raise great caution for development of PPARδ agonists in the treatment of dyslipidemias, obesity, and insulin resistance. In the future, clarifying the role of PPARδ in chronic inflammation and cancer may hold promise for development of PPARδ antagonists as new therapeutic agents in treatment of IBD and colitis-associated CRC as well as other cancers. It is essential to first evaluate whether PPARδ antagonists inhibit colonic inflammation and tumorigenesis in mouse models of IBD and CRC.

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Conflicting of interests

The authors declare that they have no conflicting of interests.

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