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MINIREVIEW

PPARδ and PGE_2 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 PGE_2 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-drevided PGE_2 signaling coordinately promote chronic colonic inflammation and colitis-associate 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-drived PGE_2

Abbreviations: PPAR, peroxisome proliferator-activated receptor; IBD, inflammatory bowel disease; CRC, colorectal cancer; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; FAP, familial adenomatous polyposis ; APC, adenomatous polyposis coli; COX-2, cyclooxygenase 2; PGs, prostaglandins; PGE-M, PGE2 metabolite; NSCLC, non-small cell lung cancer ; AOM, azoxymethane; DSS, dextran sulfate sodium.

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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 $Apc^{Min/+}$ mice [29]. The $Apc^{Min/+}$ 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 super family 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 $Apc^{Min/+}$ mouse. Another approach is to initiate colonic epithelial cell transformation by AOM in mice with a genetic predisposition to IBD such as the $Il\text{-}10^{-/-}$ 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 PGE_2 in both DSS-treated $Apc^{Min/+}$ mice and AOM-treated $Il\text{-}10^{-/-}$ mice [45]. In this study, we also found that PPARδ activation induced COX-2 expression in colonic tumor epithelial cells. COX-2-derived PGE_2 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. PGE_2 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 PGE_2 signaling pathway.

In summary, recent studies from our group and others has demonstrated that PPARδ promoted colonic inflammation and tumorigenesis. Moreover, our results suggest that PGE_2 mediates the crosstalk between colonic tumor epithelial cells and macrophages via a self-amplifying loop between PPARδ and COX-2-derived PGE_2 signaling pathways. 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.

References

1. Ekbom A, Helmick C, Zack M, and Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990; 323:1228-1233.
2. Wang D, and Dubois RN. The role of anti-inflammatory drugs in colorectal cancer. Annu Rev Med 2013; 64:131-144.
3. Burn J, Bishop DT, Chapman PD, Elliott F, Bertario L, Dunlop MG, *et al*. A randomized placebo-controlled prevention trial of aspirin and/or resistant starch in young people with familial adenomatous polyposis. Cancer Prev Res (Phila) 2011; 4:655-665.
4. Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, *et al*. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011; 378:2081-2087.
5. Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. Gastroenterology 2008;134:29-38.
6. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, *et al*. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003; 348:891-899.
7. Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, *et al*. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. Gastroenterology 2003; 125:328-336.
8. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, *et al*. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003; 348:883-890.
9. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. The lancet oncology 2012; 13:518-527.
10. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of

incident cancers during randomised controlled trials. Lancet 2012; 379:1591-1601.

11. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 2007; 356:2131-2142.
12. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA 2009; 302:649-658.
13. DuBois RN, Abramson SB, Crofford L, Gupta RA, Simon LS, Van De Putte LB, *et al*. Cyclooxygenase in biology and disease. Faseb J 1998; 12:1063-1073.
14. Newcomb PA, Baron J, Cotterchio M, Gallinger S, Grove J, Haile R, *et al*. Colon Cancer Family Registry: an international resource for studies of the genetic epidemiology of colon cancer. Cancer Epidemiol Biomarkers Prev 2007; 16:2331-2343.
15. Ogino S, Kirkner GJ, Nosho K, Irahara N, Kure S, Shima K, *et al*. Cyclooxygenase-2 expression is an independent predictor of poor prognosis in colon cancer. Clin Cancer Res 2008; 14:8221-8227.
16. Wang D, DuBois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene 2010; 29:781-788.
17. Wang D, DuBois RN. Eicosanoids and cancer. Nat Rev Cancer 2010;10:181-193.
18. Rigas B, Goldman IS, Levine L. Altered eicosanoid levels in human colon cancer. J Lab Clin Med 1993; 122:518-523.
19. Shrubsole MJ, Cai Q, Wen W, Milne G, Smalley WE, Chen Z, *et al*. Urinary prostaglandin E2 metabolite and risk for colorectal adenoma. Cancer Prev Res (Phila) 2012; 5:336-342.
20. Johnson JC, Schmidt CR, Shrubsole MJ, Billheimer DD, Joshi PR, Morrow JD, *et al*. Urine PGE-M: A metabolite of prostaglandin E2 as a potential biomarker of advanced colorectal neoplasia. Clin Gastroenterol Hepatol 2006; 4:1358-1365.
21. Cai Q, Gao YT, Chow WH, Shu XO, Yang G, Ji BT, *et al*. Prospective study of urinary prostaglandin E2 metabolite and colorectal cancer risk. J Clin Oncol 2006; 24:5010-5016.
22. Dong LM, Shu XO, Gao YT, Milne G, Ji BT, Yang G, *et al*. Urinary prostaglandin E2 metabolite and gastric cancer risk in the Shanghai women's health study. Cancer Epidemiol Biomarkers Prev 2009;18:3075-3078.
23. Kim S, Taylor JA, Milne G, Sandler DP. Association between urinary prostaglandin E2 metabolite and breast cancer risk: a prospective, case-cohort study of postmenopausal women. Cancer Prev Res (Phila) 2013; 6:511-518.
24. Morris PG, Zhou XK, Milne GL, Goldstein D, Hawks LC, Dang CT, *et al*. Increased Levels of Urinary PGE-M, a Biomarker of Inflammation, Occur in Association with Obesity, Aging, and Lung Metastases in Patients with Breast Cancer. Cancer Prev Res (Phila) 2013; 6:428-436.
25. Kekatpure VD, Boyle JO, Zhou XK, Duffield-Lillico AJ, Gross ND, Lee NY, *et al*. Elevated levels of urinary prostaglandin e metabolite indicate a poor prognosis in ever smoker head and neck squamous cell carcinoma patients. Cancer Prev Res (Phila) 2009; 2:957-965.
26. Murphey LJ, Williams MK, Sanchez SC, Byrne LM, Csiki I, Oates JA, *et al*. Quantification of the major urinary metabolite of PGE2 by a liquid chromatographic/mass spectrometric assay: determination of cyclooxygenase-specific PGE2 synthesis in healthy humans and those with lung cancer. Anal Biochem 2004; 334:266-275.
27. Mutter R, Lu B, Carbone DP, Csiki I, Moretti L, Johnson DH, *et al*. A phase II study of celecoxib in combination with paclitaxel, carboplatin, and radiotherapy for patients with inoperable stage IIIA/B non-small cell lung cancer. Clin Cancer Res 2009; 15:2158-2165.
28. Csiki I, Morrow JD, Sandler A, Shyr Y, Oates J, Williams MK, *et al*. Targeting cyclooxygenase-2 in recurrent non-small cell lung cancer: a phase II trial of celecoxib and docetaxel. Clin Cancer Res 2005; 11:6634-6640.
29. Wang D, Wang H, Shi Q, Katkuri S, Walhi W, Desvergne B, *et al*. Prostaglandin E(2) promotes colorectal adenoma growth via transactivation of the nuclear peroxisome proliferator-activated receptor delta. Cancer cell 2004; 6:285-295.
30. Siezen CL, Tijhuis MJ, Kram NR, van Soest EM, de Jong DJ, Fodde R, *et al*. Protective effect of nonsteroidal anti-inflammatory drugs on colorectal adenomas is modified by a polymorphism in peroxisome proliferator-activated receptor delta. Pharmacogenet Genomics 2006;16:43-50.
31. Peddareddigari VG, Wang D, DuBois RN. The tumor microenvironment in colorectal carcinogenesis. Cancer microenvironment 2010; 3:149-166.
32. Wang D, Wang H, Guo Y, Ning W, Katkuri S, Wahli W, *et al*. Crosstalk between peroxisome proliferator-activated receptor delta and VEGF stimulates cancer progression. Proc Natl Acad Sci U S A 2006; 103:19069-19074.
33. Zuo X, Peng Z, Moussalli MJ, Morris JS, Broaddus RR, Fischer SM, *et al*. Targeted genetic disruption of peroxisome proliferator-activated receptor-delta and colonic tumorigenesis. J Natl Cancer Inst 2009; 101:762-767.
34. Montagner A, Delgado MB, Tallichet-Blanc C, Chan JS, Sng MK, Mottaz H, *et al*. Src is activated by the nuclear receptor peroxisome proliferator-activated receptor beta/delta in ultraviolet radiation-induced skin cancer. EMBO Mol Med 2014; 6:80-98.
35. Harman FS, Nicol CJ, Marin HE, Ward JM, Gonzalez FJ, Peters JM. Peroxisome proliferator-activated receptor-delta attenuates colon carcinogenesis. Nat Med 2004; 10:481-483.
36. Hollingshead HE, Morimura K, Adachi M, Kennett MJ, Billin AN, Willson TM, *et al*. PPARbeta/delta protects against experimental colitis through a ligand-independent mechanism. Dig Dis Sci 2007; 52:2912-2919.
37. Gupta RA, Tan J, Krause WF, Geraci MW, Willson TM, Dey SK, *et al*. Prostacyclin-mediated activation of peroxisome proliferator-activated receptor delta in colorectal cancer. Proc Natl Acad Sci U S A 2000; 97:13275-13280.
38. Delage B, Rullier A, Capdepont M, Rullier E, Cassand P. The effect of body weight on altered expression of nuclear receptors and cyclooxygenase-2 in human colorectal cancers. Nutr J 2007; 6:20.
39. Takayama O, Yamamoto H, Damdinsuren B, Sugita Y, Ngan CY, Xu X, *et al*. Expression of PPARdelta in multistage carcinogenesis of the colorectum: implications of malignant cancer morphology. Br J Cancer 2006; 95:889-895.
40. Knutsen HK, Olstorn HB, Paulsen JE, Husoy T, Goverud IL, Loberg EM, *et al*. Increased levels of PPARbeta/delta and cyclin D1 in flat dysplastic ACF and adenomas in Apc(Min/+) mice. Anticancer Res 2005; 25:3781-3789.

41. Zuo X, Xu M, Yu J, Wu Y, Moussalli MJ, Manyam GC, *et al*. Potentiation of colon cancer susceptibility in mice by colonic epithelial PPAR-delta/beta overexpression. J Natl Cancer Inst 2014; 106:dju052.
42. Yuan H, Lu J, Xiao J, Upadhyay G, Umans R, Kallakury B, *et al*. PPARdelta induces estrogen receptor-positive mammary neoplasia through an inflammatory and metabolic phenotype linked to mTOR activation. Cancer Res 2013; 73:4349-4361.
43. Jeon C, Chang SC, Mu L, Zhao J, Rao JY, Lu QY, *et al*. Genetic variants of peroxisome proliferator-activated receptor delta are associated with gastric cancer. Dig Dis Sci 2013: 58:2881-2886.
44. Monk JM, Kim W, Callaway E, Turk HF, Foreman JE, Peters JM, *et al*. Immunomodulatory action of dietary fish oil and targeted deletion of intestinal epithelial cell PPARdelta in inflammation-induced colon carcinogenesis. Am J Physiol Gastrointest Liver Physiol 2012; 302:G153-167.
45. Wang D, Fu L, Ning W, Guo L, Sun X, Dey SK, *et al*. Peroxisome proliferator-activated receptor delta promotes colonic inflammation and tumor growth. Proc Natl Acad Sci U S A 2014; 111:7084-7089.