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Eicosanoid signaling in carcinogenesis of colorectal cancer

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Abstract

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death in the United States. It is of practical importance to identify novel therapeutic targets of CRC to develop new anti-cancer drugs, and to discover novel biomarkers of CRC to develop new detection methods. Eicosanoids, which are metabolites of polyunsaturated fatty acids produced by cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) enzymes, are important lipid signaling molecules involved in the regulation of inflammation and tumorigenesis. Substantial studies have shown that the profiles of eicosanoids are deregulated in CRC, and the enzymes, metabolites, and receptors in the eicosanoid signaling cascade play critical roles in regulating colonic inflammation and colon tumorigenesis. In this review, we discuss the roles of the COX, LOX, and CYP pathways in the carcinogenesis of CRC.

Keywords

eicosanoids; colonic inflammation; colorectal cancer; obesity; cyclooxygenase; lipoxygenase; cytochrome P450; soluble epoxide hydrolase

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death in the United States. It is estimated that there are ~130,000 new cases and ~50,000 deaths caused by CRC every year in the US. The five-year survival rate for CRC is >90% for early localized cancer, but drops to <5% for late-stage metastatic disease [1]. Two major risk factors of CRC are inflammatory bowel disease (IBD) and obesity, both of which are dramatically increasing in United States [2, 3]. Therefore, it is of practical importance to identify novel therapeutic targets of CRC to develop new anti-cancer drugs, and to discover novel biomarkers of CRC to develop new detection methods.

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Eicosanoids are metabolites of arachidonic acid (ARA, 20:4) produced by cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) enzymes; they are important lipid signaling molecules involved in the regulation of inflammation and tumorigenesis. Besides ARA, other polyunsaturated fatty acids (PUFAs), including linoleic acid (LA, 18:2), α -linolenic acid (ALA, 18:3), dihomo- γ -linolenic acid (DGLA, 20:3), eicosapentaenoic acid (EPA, 20:5), and docosahexaenoic acid (DHA, 22:6), are alternative substrates of these enzymes (Fig. 1). This leads to the formation of a vast array of oxylipin metabolites with diverse chemical structures and biological actions [4–6]. Substantial studies have shown that the profiles of eicosanoids are deregulated in CRC, and the enzymes, metabolites, and receptors in the eicosanoid signaling cascade play critical roles in colonic inflammation and colon tumorigenesis [7]. In this review, we will discuss the roles of the COX, LOX, and CYP pathways in the pathogenesis of colonic inflammation and CRC, as well as obesity-enhanced CRC.

Cyclooxygenases (COXs)

The metabolism of ARA by COX enzymes lead to formation of prostaglandin H_2 (PGH₂), which can be further metabolized by other enzymes involved in the COX pathway to generate various prostaglandins and thromboxane. There are two main isoforms of COX enzymes: COX-1 and COX-2. COX-1 is the major prostaglandin-producing enzyme under normal conditions. Encoded by the *PTGS1* gene, COX-1 is constitutively expressed in most cells and is involved in many basic physiological processes, such as maintaining tissue homeostasis and regulating epithelial cytoprotection [8]. Unlike COX-1, COX-2 is not expressed at basal conditions, but is stimulated by pro-inflammatory factors including hormones, growth factors, and the presence of oncogenes [8]. A recent study has also identified COX-3, a splice variant of COX-1, as a novel COX isomer. In humans, COX-3 has the most abundant expression in the cerebral cortex and heart [9], however, the detailed functional role of COX-3 remains to be further characterized.

Roles of COX-1 and COX-2 in colonic inflammation

Previous studies support that COX-1 and COX-2 play critical roles in regulating colonic inflammation. At basal conditions, neither *Cox-1*^{-/-} nor *Cox-2*^{-/-} mice developed spontaneous gastrointestinal inflammation; however, upon dextran sodium sulfate (DSS) treatment to induce acute colitis, both *Cox-1*^{-/-} and *Cox-2*^{-/-} mice developed more severe colitis compared to wild-type (WT) mice [10]. Further studies showed that *Cox-2* deletion in myeloid and endothelial cells, but not in epithelial cells, exacerbated DSS-induced colitis in mice [11]. In agreement with the data from the genetically engineered mice, treatment with COX inhibitors, in particular a combination of COX-1 and COX-2 inhibitors, exaggerated DSS-induced colitis in mice [12]. These results suggest that COX-1 and COX-2 could have protective effects against mucosal tissue injury or colonic inflammation.

Previous studies have also shown that inhibition of COX enzymes exaggerated development of colonic inflammation in another interleukin-10 knockout-induced colitis model. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), such as piroxicam and sulindac, had minimal effect on the colon in WT mice, but resulted in the rapid development

of colitis in *Il-10*^{-/-} mice; interestingly, the colitis persisted after the withdrawal of NSAID treatment. Treatment with selective inhibitors of COX-1 or COX-2 did not cause such effects in *Il-10*^{-/-} mice, but a combination of COX-1- and COX-2 inhibitors induced colitis in *Il-10*^{-/-} mice [13].

Roles of COX-1 and COX-2 in CRC

COX-1 and COX-2 share significant sequence homology and catalytic activity; however, their expression patterns in normal colon tissue and colon tumors are different [14, 15]. Human studies showed that the expression of COX-1 was relatively low in both normal colon tissue and colon tumor tissue [15]. In contrast, COX-2 expression was elevated in ~59% of adenomas and ~86% of adenocarcinomas in human CRC patients [16, 17]. In addition, higher COX-2 expression is often observed in patients with aggressive CRC and is associated with lower survival of CRC patients [14, 18]. Animal experiments showed that only COX-1, but not COX-2, was detected in normal colon tissue [19]. In addition, compared with WT mice, the colonic concentration of PGE₂ was reduced (~99% reduction) in *Cox-1*^{-/-} mice while the concentration of PGE₂ was not changed in *Cox-2*^{-/-} mice, suggesting that COX-1 is the dominant contributor responsible for the biosynthesis of PGE₂ in normal colon tissue [20]. Enhanced COX-2 expression was observed in polyps, and analysis of *Cox-1*^{-/-} and *Cox-2*^{-/-} mice support that both COX-1 and COX-2 contribute to PGE₂ production in polyps [15, 21, 22].

Animal studies support that both COX-1 and COX-2 play critical roles in the carcinogenesis of CRC. More than 80% of human CRC has an inactivating mutation of adenomatous polyposis coli (APC) [23, 24], and the mice carrying this *Apc* mutation (such as *Apc*^{Min/+} mice and *Apc*⁷¹⁶ mice) develop spontaneous intestinal tumorigenesis [25]. Compared with *Apc*^{Min/+} mice, *Cox-1*^{-/-} *Apc*^{Min/+} and *Cox-2*^{-/-} *Apc*^{Min/+} mice had reduced polyp formation (~80% reduction), supporting that both COX-1 and COX-2 could contribute to the carcinogenesis of *Apc* mutation-induced CRC [22]. Similarly, compared with *Apc*⁷¹⁶ mice, *Apc*⁷¹⁶ *Cox-2*^{+/-} mice had reduced numbers and sizes of polyps while *Apc*⁷¹⁶ *Cox-2*^{-/-} mice had even lower amounts, suggesting a dose-dependent pro-CRC effect of the *COX-2* gene in polyp formation in *Apc*⁷¹⁶ mutant mice [26]. In the azoxymethane (AOM)-induced CRC model, there were no colonic tumors formed in *Cox-2*^{-/-} mice, suggesting a role of the *COX-2* gene in AOM-induced carcinogenesis [27]. In contrast, COX-2 transgenic mice, which have higher COX-2 protein expression in the colon, developed more and larger colon tumors upon AOM stimulation [28]. Together, these results support the critical roles of COX in the carcinogenesis of CRC.

There are also inconsistent results regarding the roles of COX-1 and COX-2 in the carcinogenesis of CRC. AOM/DSS-induced CRC was not significantly changed in *Cox-1*^{-/-} mice or *Cox-2*^{-/-} mice compared with WT mice [27]. During AOM/DSS treatment, *Cox-2*^{-/-} mice had more severe body weight loss and had higher overall mortality (60% mortality for *Cox-2*^{-/-} mice versus 0% for WT mice); *Cox-1*^{-/-} mice all survived during the AOM/DSS stimulation but showed more severe body-weight loss [27]. However, we have to point out that this result may be, at least in part, caused by enhanced DSS-induced colonic inflammation in *Cox-1*^{-/-} or *Cox-2*^{-/-} mice [10, 27]. Indeed, when *Cox-2*^{-/-} mice and WT

mice were treated with multiple AOM injections to induce CRC, and without DSS stimulation, the AOM-induced CRC was completely abolished in *Cox-2^{-/-}* mice [27].

PGE₂ is an important eicosanoid produced by COX enzymes, and has been shown to have pro-inflammatory and pro-carcinogenesis effects [29]. Previous studies have shown that there was a modest increase of circulating PGE₂ in familial adenomatous polyposis (FAP) patients [30]. In another study, the preoperative plasma PGE₂ levels in CRC patients were 43% higher than in the plasma of CRC patients with benign tumors [31]. In an *in vitro* study using Caco-2 colon cancer cells, overexpression of COX-2 led to increased PGE₂ production and enhanced metastatic potential [32]. In *Apc^{Min/+}* mice, treatment with PGE₂ at the dose of 150–300 µg/mouse twice daily increased the number and size of polyps in both the colon and small intestine; in addition, PGE₂ treatment increased phosphorylation of Akt to promote cancer cell growth and reduced apoptotic cells in polyps [33]. In a CRC xenograft tumor model, treatment of PGE₂ increased tumor growth and stimulated tumor angiogenesis, via a CXCL1-dependent mechanism [34]. PGE₂ acts through different prostaglandin E₂ receptor (EP) receptors (EP1, EP2, EP3, and EP4) [35]. It has been shown that the absence of EP1 receptors significantly reduced CRC in both the AOM/DSS-induced CRC model and *Apc^{min}* mouse model [36–39]. Genetic ablation of EP4 resulted in ~56% reduction of AOM-induced aberrant crypt foci (ACF) [40]. Together, these results support that PGE₂ may directly promote tumorigenesis of CRC, and therefore could contribute to the tumor promoting effects of COX-2.

Animal and human studies support that pharmacological inhibitors of COX enzymes (COXIBs) reduce the risks of CRC. Treatment of the COXIBs MF tricyclic and rofecoxib reduced intestinal polyps in *Apc⁷¹⁶* mice [26, 41]. Similarly, treatment of sulindac sulfide, which inhibits both COX-1 and COX-2 (IC₅₀ = 14.9 nM for COX-1, and IC₅₀ = 1.2 nM for COX-2), inhibited intestinal polyps formation in *Apc⁷¹⁶* mice and *Apc^{Min/+}* mice [26, 42]. In an AOM-induced colon cancer model in rats, dietary feeding of 1500 ppm celecoxib reduced colonic tumor incidence, multiplicity, and burden by 87–97% [43]. Human clinical trials also support that COX inhibitors have anti-CRC effects. COX inhibitors, such as celecoxib and sulindac, have been shown to reduce adenomas in FAP patients. The Prevention of Colorectal Sporadic Adenomatous Polyps trial showed that a daily intake of Celebrex at a single dose of 400 mg/day significantly reduced the occurrence of colorectal adenomas within three years after polypectomy in sporadic colon cancer patients [44]. A recent Phase III trial in children aged 10–17 with FAP showed that treatment with celecoxib for 5 years at a dose of 16 mg/kg/day was associated with a lower rate of polyposis and longer disease progression time [45]. Together, these results support that COX inhibitors could be effective agents for prevention and/or treatment of CRC.

Although many studies have demonstrated that COX inhibitors reduce the risks of CRC, long-term high-dose use of these drugs could cause life-threatening cardiovascular risks which greatly limit the applications of these drugs for CRC prevention [46]. There are at least two mechanisms to explain the cardiovascular toxicities of COX inhibitors. The first mechanism of cardiovascular toxicity is that these drugs could efficiently block the formation of COX-2-derived prostacyclin (PGI₂) which is a potent vasodilator, but not COX-1 derived thromboxane A₂ (TXA₂) which is a potent vasoconstrictor; therefore, the

resulted decrease of the PGI₂ to TAX₂ ratio may cause thrombotic cardiovascular events [47]. Consistent with this mechanism, previous studies showed that a 6-h treatment of celecoxib or rofecoxib significantly reduced the ratio of PGI₂ (analyzed using stable metabolite 6-keto-prostaglandin F_{1α}) to TXA₂ (stable metabolite thromboxane B₂) in the plasma of mice [48]. The second mechanism of toxicity is that these drugs could suppress COX-mediated metabolism of 20-hydroxyeicosatetraenoic acid (20-HETE), a potent vasoconstrictor, thus leading to high circulating levels of 20-HETE. Indeed, Liu et al. showed that chronic high-dose use of rofecoxib caused a ~100-fold increase of the plasma concentration of 20-HETE. This mechanism could potentially explain the cardiovascular risks of COX inhibitors, including both NSAIDs and COXIBs [49].

Roles of other enzymes in the COX pathway in CRC

Since COX-2 inhibitors are associated with potential adverse effects, there is increased interest to study the roles of COX down-stream enzymes in CRC. In the COX pathway, ARA is metabolized by COX enzymes to form PGH₂, which can be further metabolized by prostaglandin E synthases (PGES), including microsomal PGES-1 (mPGES-1), microsomal PGES-2 (mPGES-2) and cytosolic PGES (cPGES), to produce PGE₂ [50].

The mPGES-1 enzyme, which is a membrane-associated protein, is expressed at low levels in most tissues, but can be induced by pro-inflammatory cytokines or under tumorigenic conditions [51, 52]. For example, the expression of mPGES-1 can be induced *in vitro* by TNF-α in HCA7 human colonic adenocarcinoma cells [52]. Compared to paired normal colon tissues, the expression of mPGES-1 was found to be increased in ~83% tumorous colon tissues [52], suggesting that the expression of mPGES-1 is upregulated in human CRC. Inhibition of mPGES-1 has been shown to reduce colon carcinogenesis *in vitro* and *in vivo*. Treatment with PGES-1-specific antisense oligonucleotide reduced HCA7 human colonic adenocarcinoma cell growth and PGE₂ production; in contrast, overexpression of mPGES-1 in HCA7 cells increased cell growth [53]. Compared with *mPGES-1*^{+/+} mice, *mPGES-1*^{-/-} mice had attenuated AOM-induced CRC with reduced ACF formation and nuclear expression of β-catenin in the colon [54]. Additionally, compared with *Apc*^{14/+} mice, *Apc*^{14/+} *mPGES-1*^{+/+} mice had a ~66% reduction of intestinal polyps and ~51% reduction of colonic polyps, supporting that mPGES-1 contributes to the carcinogenesis of *Apc* mutation-induced CRC [54].

A series of mPGES-1 inhibitors have demonstrated promising effects in inhibiting cancer growth and other diseases due to its inhibition of PGE₂ synthesis. Treatment with mPGES-1 inhibitor MK-886 reduced cell growth and PGE₂ production in HCA7 human colonic adenocarcinoma cells [53]. MK-886 also reduced the cell growth and colony formation of U87-MG human astrogloma cells [55]. AF3485, a human mPGES-1 inhibitor, has been shown to inhibit A431 human epidermoid carcinoma cell growth in mice by suppressing angiogenesis in a xenograft cancer model [56]. Treatment with MF63, another selective mPGES-1 inhibitor, inhibited colony formation of DU145 and PC-3 prostate cancer cells at 10 μmol/L after 48 h [57]. mPGES-1 inhibitor MF63 also showed anti-hyperalgesia effects. Administration of MF63 at a dose of 10–100 mg/kg inhibited LPS-induced thermal hyperalgesia in humanized mPGES-1 knock-in (KI) mice and guinea pigs [58]. Moreover,

treatment with MF63 at a dose of 30 mg/kg inhibits monosodium iodoacetate-induced osteoarthritic pain in guinea pig [58]. Together, mPGES-1 inhibitors are promising therapeutic molecules for disease treatments.

Compared with mPGES-1, the roles of mPGES-2 and cPGES in CRC are less studied. Unlike mPGES-1, mPGES-2 is not induced by pro-inflammatory mediators [59], but is constitutively expressed in a variety of tissues, such as brain, heart, skeletal muscle, kidney, and liver [60]. mPGES-2 is a Golgi membrane-associated protein that works with COX-1 and COX-2 to produce PGE₂ [59]. However, in *mPGES-2* knockout mice, there is no alteration in PGE₂ levels in several tissues, such as lung, kidney, heart, and brain, compared with wild-type mice, suggesting mPGES-2 is not essential for PGE₂ synthesis under basal conditions [61]. Similar to mPGES-2, cPGES is also expressed in a ubiquitous manner, and is mainly linked with COX-1 to regulate PGE₂ biosynthesis [62]. RNA blot analysis showed that cPGES is most abundantly distributed in the testes [62]. cPGES gene deletion causes poor lung development and growth retardation, resulting in perinatal lethality in mice [63].

Lipoxygenases (LOXs)

Lipoxygenases (LOXs) catalyze the conversion of PUFAs to form leukotrienes and hydroxyl fatty acids. There are six functional LOX genes in the human genome, including *Alox15*, *Alox15B*, *Alox12*, *Alox12B*, *Alox5*, and *Alox5*, which encodes six LOX isoforms: 15-LOX, 15-LOX-2, 12-LOX, 12R-LOX, eLOX-3 and 5-LOX, respectively [64]. The expressions of LOX enzymes have been found in many cell types, such as immune, epithelial, and tumor cells, and previous studies have shown that LOX enzymes play critical roles in regulating inflammation, immune responses, and tumorigenesis [65]. The expressions of LOX enzymes can be found not only in mammals but also in plants [66].

Roles of 15-LOX in CRC

Previous studies showed that the expression of 15-LOX-1 and the concentration of its eicosanoid metabolites were reduced in human colorectal polyps and tumors [67]. It is reported that ~87% (12 out of 15) of patients with hereditary FAP had reduced expression of 15-LOX-1 in colorectal adenomas [68]. Patients with sporadic polyps were also reported to have decreased expression of 15-LOX-1 in colorectal adenomas and carcinomas [69]. Previous studies showed that compared with healthy control patients (age = 55.8 ± 7.5 years, n = 40), the serum concentrations of 15S-HETE, a metabolite of ARA produced by 15-LOX-1, were significantly ($P < 0.001$) reduced in CRC patients (age = 60.3 ± 13.3 years, n = 52) [70]. These results are consistent with the reduced expression of 15-LOX-1 in CRC patients and suggest that the circulating concentrations of 15S-HETE might be used as a potential biomarker of CRC. In agreement with this study, Shureiqi et al. showed that the concentrations of 13-hydroxyoctadecadienoic acid (13-HODE), a metabolite of LA produced by 15-LOX-1, was lower in colorectal adenomas compared to non-neoplastic colorectal mucosa [5.94 ± 3.28 ng/μg protein (mean ± SD) versus 63.52 ± 34.46 ng/μg protein, $P = 0.0021$] [68]. In addition, the colonic concentrations of 13-HODE were reduced in CRC mucosa compared with paired normal colon mucosa [71]. Together, these results demonstrate that the 15-LOX-1 pathway is downregulated in CRC.

Regarding the functional roles of 15-LOX-1 in the carcinogenesis of CRC, previous studies showed that compared with WT mice, mice with intestine-specific expression of human 15-LOX-1 had reduced development of AOM/DSS-induced CRC, suggesting that 15-LOX-1 has an anti-CRC effect [72]. 15-LOX-1 could suppress CRC through multiple possible mechanisms. Intestinal expression of 15-LOX-1 suppressed activation of NF- κ B, which plays a key role in regulating tumorigenesis, inflammatory and autoimmune diseases, by decreasing the expression of TNF- α in colonic epithelial cells [72]. Hong et al. reported that 15-LOX-1 overexpression in HCT-116 human CRC cells inhibited cell growth by inducing p53 phosphorylation [73]. The anti-CRC effects of 15-LOX-1 could be, at least in part, mediated by its oxylipin metabolites, notably 15-HETE and 13-HODE. Treatment with 15-HETE inhibited cell proliferation and induced apoptosis in HT-29 human colon cancer cells, via a PPAR γ -dependent pathway [74]. 13-HODE has been shown to inhibit proliferation and induce apoptosis through down-regulating PPAR- in DLD-1 and RKO cell lines [67]–[75].

Roles of 12-LOX in CRC

12-LOX is a LOX isoform expressed in epithelial cells and myeloid cells including platelets [65]. Many mutations of 12-LOX are found in epithelial cancers, suggesting a potential link between 12-LOX and tumorigenesis [65]. Wen et al. found that the genes encoding 12-LOX are shown to be genetically polymorphic, which may affect the expression or activity of 12-LOX and consequently contribute to variation in individual susceptibility to cancer through aberrant ARA metabolism [76]. Genotypes of 12-LOX polymorphisms were determined in 1000 CRC patients and 1300 healthy controls, and the results showed that 12-LOX 261Gln/Gln genotypes in patients are over-represented compared with controls (28.7 versus 23.7%; adjusted OR = 1.38, 95% CI = 1.09–1.74; $P < 0.01$) [76]. In addition, the 12-LOX 261Gln/Gln genotype carriers have significantly higher platelet 12-LOX activity compared with the 12-LOX Arg/Arg genotype carriers [76]. These observations indicate that inherited polymorphisms in eicosanoid signaling may confer susceptibility to CRC. However, there is no direct evidence showing that the expression of 12-LOX is changed in CRC patients or CRC animal models.

Cell culture studies support that 12-LOX could contribute to carcinogenesis of CRC. Over-expression of 12-LOX in human colon cancer cells (Caco2 and SW480) enhanced cell migration [77], suggesting that 12-LOX could induce an invasive phenotype in CRC cells. 12-HETE, a metabolite of 12-LOX produced from ARA, has been implicated in angiogenesis and tumor invasion in several tumor types including CRC [77]. Colon cancer cell-derived 12-HETE induces retraction of cancer-associated fibroblasts via Ca²⁺ signaling, which indicates that 12-HETE may enhance invasiveness of CRC [78].

Roles of 5-LOX in CRC

Many studies showed that 5-LOX is over-expressed in colon cancer cells, animal models of CRC, and human CRC patients. The expression of 5-LOX is detected in colon cancer cell lines, such as LoVo, HCT116, and HT29 [79]. Compared with WT mice, Apc⁴⁶⁸ mice had increased expression of 5-LOX in intestinal lymphoid tissue [80]. In addition, treatment with AOM increased 5-LOX activity in rat colons [81]. These results demonstrate that the

expression of 5-LOX is upregulated in animal models of CRC. Human studies also showed that the expression of 5-LOX was upregulated in adenomatous polyps and colon cancers compared with normal colonic mucosa [79, 82, 83]. Soumaoro et al. analyzed gene expression of 5-LOX in paired colorectal tumor and adjacent normal mucosa samples, and found that ~73% samples showed higher 5-LOX mRNA levels compared to paired normal mucosa samples [83]. Together, these results showed that the 5-LOX pathway is upregulated in CRC.

The expression of 5-LOX and the concentrations of 5-LOX-produced oxylipin metabolites were also increased in the colon tissues of IBD patients. Compared with control subjects (n = 9), the colonic biopsies from patients with active IBD (n = 17) had 3–7-fold higher numbers of cells expressing 5-LOX (P = 0.03) [84]. Sharon et al. showed that the concentration of leukotriene B₄ (LTB₄) in the mucosa from IBD patients (n = 6) versus mucosa from healthy subjects (n = 4) were 254 ± 116 ng/g versus <5 ng/g (P < 0.0005) [85]. Kim et al. showed that the urinary concentrations of Leukotriene E₄ (LTE₄) were elevated in children with active Crohn's disease compared with subjects with inactive disease or control subjects [84]. Together, these results show that the 5-LOX pathway is upregulated in IBD.

Regarding the functional roles of 5-LOX in the carcinogenesis of CRC, Cheon et al. showed that compared with *Apc*⁴⁶⁸ *5-lox*^{+/+} mice, *Apc*⁴⁶⁸ *5-lox*^{-/-} mice had reduced polyp burden and increased macrophage infiltration into the tumor [86], which indicates 5-LOX may impact tumor immunity. Eric et al. demonstrated that mice lacking hematopoietic expression of 5-LOX exhibited reduced recruitment of myeloid-derived suppressor cells (MDSCs) to the spleen, mesenteric lymph nodes, and primary tumor site [80]. In agreement with these studies, treatment with Zileuton, a 5-LOX inhibitor and approved drug to treat asthma [87], reduced polyps and decreased systemic and polyp-associated inflammation in *Apc*⁴⁶⁸ mice [88]. Treatment with another 5-LOX inhibitor, Rev-5901, decreased cell proliferation, increased apoptosis, and inhibited DNA synthesis in the Lovo colon cancer cells [79]. Together, these results support that 5-LOX could be a therapeutic target of CRC, and inhibitors of 5-LOX could be used for prevention of CRC.

Many studies showed that the oxylipin metabolites of 5-LOX have pro-inflammatory and pro-CRC effects, supporting that the pro-CRC effects of 5-LOX could be mediated by its metabolites. In addition, subcutaneous injections of Leukotriene D₄ (LTD₄) (24.8 µg/kg/day) increased primary tumor growth of CRC in nude mice [89]. LTD₄ could increase the tumorigenesis of CRC through several possible mechanisms, such as enhancing proliferation and migration of colon cancer cells, activating β-catenin and COX-2, and increasing immune cell infiltration [89]–[90]. Moreover, the small intestinal tumors of *Apc*^{Min/+} mice produced significantly higher levels of LTB₄ in 101- and 115-day-old mice compared with small intestinal tissues of normal mice [91]. An *in vitro* study showed that LTB₄ can increase the proliferation rate of HT-29 and HCT-15 human colon carcinoma cells in a time- and concentration-dependent manner [92]. Together, these results show that the pro-CRC effects of 5-LOX could be mediated by its metabolites.

Roles of Cysteinyl leukotriene receptor (CysLTR1) signaling in CRC

Cysteinyl leukotriene receptor (CysLTR) signaling is initiated upon binding cysteinyl leukotrienes (such as LTC₄, LTD₄) to two G-protein-coupled receptors (GPCRs), CysLTR1 and CysLTR2 [93, 94]. The expression of CysLTR1 has been reported to be increased in CRC, and high expression of CysLTR1 in tumors was associated with a reduced survival prognosis in CRC patients [95]. In agreement with this study, the microarray results of 329 CRC patient tissues showed that high nuclear expression of CysLTR1 is associated with a poor prognosis [96]. In terms of the functional roles of CysLTR1 in CRC, previous studies showed that compared with *Apc*^{Min/+} littermates, *Apc*^{Min/+}*Cysltr1*^{-/-} mice had reduced intestinal tumorigenesis, suggesting that CysLTR1 has pro-CRC effects [97]. In an AOM/DSS-induced CRC model, the colonic polyps of *Cysltr1*^{-/-} mice exhibited low-grade dysplasia while the polyps from WT mice had an adenoma-like phenotype [98]. Moreover, the colonic polyps of *Cysltr1*^{-/-} mice showed a significant decrease in nuclear β -catenin and COX-2 protein expression [97]. These results indicate potential pro-tumorigenic activities of CysLTR1 in CRC.

Roles of the CYP pathway in CRC

PUFAs can also be metabolized by CYP monooxygenases (largely CYP2C and CYP2J isoforms), leading to the formation of oxylipin metabolites termed fatty acid epoxides. Fatty acid epoxides are metabolically unstable (with a half-life of several seconds *in vivo*), and are rapidly metabolized by soluble epoxide hydrolase (sEH) to generate the corresponding fatty acid diols [6]. Previous studies showed that fatty acid epoxides, in particular epoxyeicosatrienoic acids (EETs), have anti-inflammatory effects, while fatty acid diols are usually biologically inactive or pro-inflammatory [6, 99]. Therefore, the sEH enzyme is widely regarded as a pro-inflammatory enzyme, and is a therapeutic target of many human disorders [6]. Currently pharmaceutical companies and academic laboratories are developing sEH inhibitors for clinical applications [100, 101].

Emerging evidence supports that sEH could contribute to the pathogenesis of IBD and CRC. Enayetallah et al. showed that sEH was detected in ~40% of human colon adenocarcinoma (detected in 7 out of 17 samples) with relatively high expression levels, but was not detected in matched benign samples (0 out of 4 samples) [102]. Zhang et al. also showed that the expression of sEH is increased in ulcerative colitis-associated dysplasia and adenocarcinoma [103]. These results support that sEH is overexpressed in IBD and CRC, which is in agreement with the proinflammatory effect of sEH. Regarding the functional roles of sEH in colonic inflammation and CRC, previous studies showed that inhibition of sEH caused beneficial effects in these two diseases. Compared with WT mice, DSS-induced colonic inflammation is reduced in *sEH*^{-/-} mice [103]. Pharmacological inhibition or genetic ablation of sEH also reduced colonic inflammation and CRC in *IL-10*^{-/-} mice [104, 105]. Together, these results support that sEH could promote colonic inflammation and colon cancer.

The roles of CYP monooxygenases (largely CYP2C and CYP2J) in CRC are largely unknown. Enayetallah et al. showed that CYP2C9 is detected with high expression levels in

most samples of human colon adenocarcinoma (detected in 13 out of 17 samples), but is not detected in matched benign samples [102]. No study has investigated the functional roles of CYP monooxygenases in CRC. In other cancer types, previous studies have shown the cancer promoting effects of CYP monooxygenases. For example, compared with WT mice, genetically engineered mice with overexpression of CYP monooxygenases had accelerated xenograft tumor growth of B16F10 melanoma and T241 fibro sarcoma [106]. Further studies are needed to characterize the roles of CYP monooxygenases and their metabolites in CRC.

Roles of eicosanoid signaling in obesity-enhanced CRC

Obesity is a major health concern in the US: more than one-third of American adults (34.9% or 78.6 million) are obese [107]. Obese individuals have a 30–60% greater risk of developing CRC and late-stage CRC [108]. Due to the obesity epidemic and potential lethal consequence of CRC, obesity-enhanced CRC is a serious health problem in the US. To date, the mechanism by which obesity increases the risk for CRC is not well understood [109], and there are few effective strategies to prevent or treat obesity-enhanced CRC.

We recently used a LC-MS/MS-based lipidomics to study the roles of eicosanoids in obesity-induced colonic inflammation, which is a major factor of CRC [110]. We found that obesity-induced colonic inflammation is associated with overexpression of sEH and its metabolites in the colon. Indeed, the concentrations of sEH-produced fatty acid diols were significantly increased in the colon of obese mice. These fatty acid diols include ARA-derived 8,9-, 11,12-, and 14,15-dihydroxyeicosatrienoic acids (DHETs); EPA-derived 17,18-dihydroxyeicosatetraenoic acid (DiHETE); and DHA-derived 7,8-, 10,11-, 16,17-, and 19,20- dihydroxydocosapentaenoic acid (DiHDPE). In addition, we found that pharmacological inhibition or genetic ablation of sEH abolishes obesity-induced colonic inflammation and activation of the Wnt signaling pathway, which are early events involved in the carcinogenesis of CRC and play important roles in the initiation and promotion of CRC [110, 111]. Together, these results support that obesity induces colonic inflammation through up-regulation of sEH in colon, and targeting sEH could be a promising strategy for prevention of obesity-induced colonic inflammation and associated diseases such as CRC.

Besides the sEH pathway, we also found that the expression of COX-2 and the concentrations of COX-2-produced metabolites, such as PGE₂, PGD₂, and PGF_{2α}, were significantly increased in colon of obese mice. Considering the essential roles of COX-2 in inflammation and tumorigenesis, this result suggests that COX-2 could also contribute to the pathogenesis of obesity-enhanced CRC. Notably, the Colorectal Adenoma/Carcinoma Prevention Program 2 (CAPP2) study showed that a daily intake of aspirin, a pharmacological inhibitor of COX enzymes, abrogated obesity-enhanced CRC in patients with Lynch syndrome at the dose of 600 mg per day [112], suggesting that targeting COX could be a therapeutic target for obesity-enhanced CRC.

Since both sEH and COX-2 are upregulated in the colon of obese mice, co-inhibition of these two pathways could achieve enhanced efficacy. Our previous studies showed that co-administration of sEH inhibitors and COX-2 inhibitors synergistically suppressed inflammation, pain, primary tumor growth, and tumor metastasis, with reduced COX-2

inhibition-induced cardiovascular toxicities [48, 113]. This co-administration strategy could reduce the required doses of COX-2 inhibitors, and therefore attenuate the risks resulting from the usage of COX inhibitors. In addition, we have designed first-in-class COX-2/sEH dual inhibitors, and showed that they have potent anti-cancer and anti-metastatic effects [113]. It would be important to test whether inhibition of both COX-2 and sEH could generate more effective suppression of obesity-induced colonic inflammation and associated CRC.

Summary

In the US, there are ~130,000 new cases and ~50,000 deaths caused by CRC every year, making CRC a serious health problem [1]. It is important to identify novel therapeutic targets of CRC, in order to develop effective methods for prevention and/or treatment of CRC. Substantial studies have shown that the metabolites, enzymes, and receptors involved in the eicosanoid signaling contribute to the carcinogenesis of CRC. This notion is best demonstrated by the findings that COX-2 is over-expressed in most human CRC, and COX-2 inhibitors are among the most effective agents for CRC prevention [7, 114]. It would be important to discover novel therapeutic targets from the eicosanoid signaling cascade, such as other enzymes involved in the COX-2 pathway, or the CYP/sEH pathway, in order to develop novel agents to reduce the risks of CRC.

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Fig. 1. Metabolism of ARA by COX, LOX, and CYP enzymes leads to formation of eicosanoid metabolites. Besides ARA, other fatty acids are also alternative substrates of these enzymes, leading to formation of an large array of oxylipin metabolites with diverse chemical structures and biological actions.