Published in final edited form as:

Curr Colorectal Cancer Rep. 2012 December ; 8(4): 316–324. doi:10.1007/s11888-012-0146-1.

Lipoxygenase and Cyclooxygenase Pathways and Colorectal Cancer Prevention

Chinthalapally V. Rao, Naveena B. Janakiram, and Altaf Mohammed

Center for Cancer Prevention and Drug Development, Medical Oncology, Department of Medicine, PC Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA

Abstract

Colorectal cancer is one of the commonest malignancies in both men and women. In spite of significant progress in screening and in surgical and therapeutic interventions, colorectal cancer (CRC) is still a major public health problem. Accumulating evidence suggests that targeting inflammatory pathways may provide protection against the development of CRC. Eicosanoids derived from the enzymes cyclooxygenase (COX) and lipoxygenase (LOX) may contribute to CRC carcinogenesis. Approaches for targeting COX-1 and COX-2 with traditional nonsteroidal anti-inflammatory agents or targeting COX-2 with specific inhibitors are highly successful at the preclinical and clinical levels; however, large-scale clinical applicability of these agents is limited owing to unwanted side effects. Emerging studies suggest that 5-LOX-derived leukotrienes may contribute to colon tumor development and risk of thrombotic events. Thus, developing drugs that target both 5-LOX and COX-2 may provide a safer strategy. In this review, we discuss evidence for the involvement of 5-LOX in colon tumor development and targeting 5-LOX and COX-2 with synthetic and naturally occurring agents for CRC prevention.

Keywords

Lipoxygenase; Cyclooxygenase; Nonsteroidal anti-inflammatory drugs; Eicosanoid; Chemoprevention; Dual cyclooxygenase/lipoxygenase inhibitors; Curcumin; Resolvins; Omega-3 fatty acids

Introduction

Colorectal cancer (CRC) is one of the commonest human malignancies in the Western world, including the USA. Recently it was reported that approximately 1.2 million men and women are diagnosed with CRC annually and that more than 600,000 individuals die annually of this cancer worldwide; thus, CRC is a major public health problem [1]. Epidemiological and animal model studies indicate that the cause of colon cancer is multifactorial and complex [2-4]. Strategies for cancer prevention involving reduction or elimination of human exposure to environmental carcinogens may not always be effective because significant portions of the human cancer burden may be due to endogenously formed carcinogens, co-carcinogens, and promoters [5]. Inhibition of cancer development by administration of chemicals that directly and/or indirectly reduce the cancer-producing

Address for Correspondence: Chinthalapally V. Rao, Ph.D. George Lynn Cross Research Professor Director, Center for Cancer Prevention and Drug Development 975 NE 10th Street, BRC 1203, OUHSC Oklahoma City, OK 73104, USA Tel.: +1-405-2713224/+1-405-3976151 Fax: +1-405-2713225 cv-rao@ouhsc.edu.

Disclosure No potential conflicts of interest relevant to this article were reported.

effects of genotoxic and promoting substances offers an alternative approach to cancer prevention. Chemopreventive strategies and agents that can retard, block, or reverse the process of carcinogenesis are urgently needed for people with precancerous lesions, those diagnosed at early stages, and subgroups with a particular genetic susceptibility to cancer. Recent advances in the understanding of cancer biology at cellular and molecular levels have led to identification of important signaling components that can be targeted by newly developed chemopreventive agents [6-10].

Inflammation and Nonsteroidal Anti-inflammatory Drugs

Over the past few decades, preclinical, clinical, and extensive mechanistic studies have supported the importance of inflammatory mediators, particularly inflammatory cytokines and arachidonic acid (AA)-derived eicosanoids, in the pathogenesis of CRC. [11]. Evidence indicates that colorectal tumors are infiltrated by various types of immune cells, including neutrophils, mast cells, natural killer cells, dendritic cells, and tumor-associated macrophages. They exhibit overexpression of inflammatory genes, including cyclooxygenase (COX)-2, nuclear factor B, Stat3, inducible nitric oxide synthase, and inflammatory cell infiltration is a hallmark of colorectal tumor progression [12, 13]. Epidemiological and clinical trial studies support the importance of nonsteroidal anti-inflammatory drugs (NSAIDs) in the reduction of the risk of colon cancer [11, 12]. Unequivocal evidence for the inhibitory effects of several NSAIDs on CRC was provided by our laboratory and others using animal models of colon cancer [12-16]. Most regular NSAIDs block prostaglandin E₂ (PGE₂) formation by inhibiting COX-1 and COX-2 activities. Among all of the NSAIDs, aspirin has been most extensively studied at clinical (both observational and randomized) and preclinical levels and has been found to have colon cancer chemopreventive properties [13, 17-20]. A recently published study [21] supports the usefulness of aspirin for prevention of CRC and other cancers. This randomized trial, involving over 25,000 people, compared daily use of aspirin against no aspirin and showed that long-term (20-year) use of aspirin decreased the risk of CRC by 40%, decreased the risk of lung cancer by 30%, and, remarkably, decreased the risk of esophageal cancer by 60%. Use of aspirin for 5 years or longer reduced the risk of proximal colon cancer by about 70% ($p < 0.0001$). This finding is especially significant because of the association of serrated polyps in the proximal colon with the greater difficulty in diagnosing these proximal polyps by colonoscopy screening. Preclinical studies from our laboratory and others have shown that administration of aspirin significantly inhibits the formation of chemically induced colonic tumors in rodent models [20, 22].

COX-2 and CRC Prevention

The role of COX-2 in colon tumorigenesis has been well established and served as the rationale for development of selective COX-2 inhibitors. Studies from our laboratory and others have shown that the selective COX-2 inhibitor celecoxib suppresses colon cancer development much more efficiently than the nonselective COX inhibitors and that it has fewer side effects [23, 24]. COX-2-selective inhibitors definitely hold advantages over COX-1 inhibitors because of their limited gastrointestinal toxicity [25]. Clinical trials with celecoxib and rofecoxib have shown that these agents provide significant chemopreventive efficacy against sporadic polyp development; however, the requirement of high doses and the increased occurrence of cardiovascular events have been deterrents for widespread clinical application [26-28]. Long-term clinical observations suggest that COX-2-selective inhibitors may contribute to increased cardiovascular risk in individuals with prothrombotic conditions [29, 30]. Thus, use of various COX-2 inhibitors at high doses may not be a fruitful approach for the prevention and treatment of sporadic colon cancer, which represents more than 80% of total CRC. In addition, inhibition of COX activity leads to a shift from the

AA pathway to the 5-lipoxygenase (5-LOX) pathway and formation of protumorigenic and prothrombotic metabolites [31] (illustrated in Fig. 1). It is important to develop new strategies that target 5-LOX and COX-2 to gain maximal efficacy without unwanted side effects, particularly prothrombotic effects that pose a risk of fatal cardiovascular events.

5-LOX Metabolites, Inflammation, and Colon Carcinogenesis

In recent years, a critical role of 5-LOX in the regulation of cell proliferation and apoptosis has emerged [32-34]. A number of reports document that 5-LOX is overexpressed in cancer cells and human tumors, including those of the colon, lung, breast, prostate, pancreas, bone, brain, and mesothelium [36-39]. In vitro and nude mouse studies indicate that 5-LOX overexpression is associated with increased proliferation and tumor growth [40]. Studies by Ohd et al. [34] show that human colon adenocarcinomas overexpress 5-LOX and possess higher levels of leukotrienes and suggest that patients with overexpression of 5-LOX and cysteinyl leukotriene receptors had relatively poor survival. Thus, upregulated 5-LOX expression appears to be associated with neoplastic transformation, although the sequence of events connecting 5-LOX gene expression to colon cancer development is unknown. A role for COX-2 in colon tumorigenesis has been well established through use of COX-2 knockout mice models [41, 42]. However, comparable information with 5-LOX knockout mice in colon carcinogenesis is lacking.

Ding et al. [43] found that 5-LOX messenger RNA is expressed in cancer cells but not in normal cells. They used an antisense method to block 5-LOX expression and confirmed a role of 5-LOX in promoting cancer cell proliferation. Adding the 5-LOX product 5-(S)-hydroxyeicosatetraenoic acid [5-(S)-HETE] reversed the beneficial effects of the 5-LOX antisense. 5-LOX inhibitors can also inhibit the growth of mouse colon adenocarcinoma cell lines in vitro and in vivo [44, 45]. Several studies suggest that activation of 5-LOX, with accumulation of 5-(S)-HETE and leukotrienes, is triggered by colon-tumor-promoting bile acids and carcinogens [47]. Previously, we have shown that treatment of rats with the colon carcinogen azoxymethane (AOM) leads to increased activity of 5-LOX in the colon [48, 49].

5-LOX converts AA to 5-(S)-HETE, which in turn is converted to leukotriene A₄ (LTA₄) and then to leukotriene B₄ (LTB₄) by LTA₄ hydrolase [50] (Fig. 1). This process requires the activity of the additional enzyme 5-LOX-activating protein (FLAP) [51], and the translocation of 5-LOX into the nuclear membrane [52]. The exact mechanism by which 5-LOX or its metabolites regulate cell proliferation and apoptosis is not fully established. LTB₄ has been shown to inhibit apoptosis [46]. A possible mechanism by which 5-LOX metabolites could regulate colon tumor cell growth is through their electrophilic activity and generation of reactive lipid metabolites, which can impair translocation of the transcription factor p53 to nuclei. We and others have shown previously that electrophilic prostaglandins dose-dependently induce the accumulation of p53 in cytosol rather than in nuclei of colon cancer cell lines, and that COX-2-selective inhibitors can reverse the cytosolic p53 accumulation [53]. The prevention of p53 nuclear accumulation by electrophiles might represent a mechanism by which 5-(S)-HETE, leukotrienes, and prostaglandins suppress p53-mediated apoptosis in colon carcinogenesis.

The physiological role of 5-LOX in cells of the myeloid lineage has been studied extensively [52, 53]; however, abnormal overexpression, which leads to inflammation and prothrombotic and protumorigenic effects, has come under investigation only recently [54-56]. 5-LOX is a dioxygenase and converts AA to 5-(S)-hydroperoxyeicosatetraenoic acid and 5-(S)-HETE. 5-(S)-Hydroperoxyeicosatetraenoic acid is converted to LTA₄, and this can be metabolized further by different routes to LTB₄, leukotriene C₄, leukotriene D₄, or leukotriene E₄ or alternatively to lipoxins [57, 58]. Leukotrienes play a major role in the

inflammatory process and are implicated in a number of inflammatory diseases [59, 60,]. LTB₄ is a potent stimulator of leukocyte activation, and adhesion of these cells to vascular endothelium elicits chemokinetic and chemotactic responses [61-64]. Mehrabian and colleagues have demonstrated that inflammatory eicosanoids derived from increased 5-LOX expression—LTB₄ and the cysteinyl leukotrienes—are active in the vasculature during thrombosis. They have been shown to promote inflammatory cell activation, cell proliferation, and vasoconstriction [65, 66].

Balancing of COX and Lipoxygenase Pathways

Generally, use of COX-2 inhibitors suppresses COX-2-dependent production of the antithrombotic prostacyclin (PGI₂) in endothelial cells; but under normal conditions, COX-2 inhibition has only a marginal effect on the net antithrombotic balance owing to the importance of COX-1 as a source of PGI₂ in the normal state. However, in the setting of inflammatory conditions, e.g., atherosclerosis, COX-2 plays a greater role as a source of PGI₂ and more platelet-derived thromboxane A₂ is also produced; thus, inhibiting COX-2 has a more profound effect on prostanoid balance, favoring platelet-dependent thrombosis [67, 68]. The shifting of the flux of arachidonate through the 5-LOX pathway by inhibiting COX activity is of major importance in the increased cardiovascular risks associated with COX-2-selective inhibitors. The exact molecular mechanisms by which COX-2 inhibition leads to increased prothrombotic effects is yet to be fully understood; but, several studies support a role for 5-LOX-derived metabolites in prothrombotic effects [69, 70].

Clinical observations suggest that prolonged administration of COX-2 inhibitors is required to modify thrombotic risk, and a reasonable culprit for the aberrant thrombotic response is the platelet [71, 72]. With COX-2 inhibition, there is an increase in the number of coated platelets, which have exposed phosphatidylserine and retention of several procoagulant proteins on the their surfaces; and these coated platelets support a robust prothrombinase activity [73-75]. The consequences of too many coated platelets remain speculative in preclinical models, but the prothrombotic characteristics of coated platelets suggest that they have the potential to induce thrombotic responses. Some studies suggest that chronic stimulation of the immune system or inflammation might be a cause of elevated numbers of coated platelets [76]. Given the anti-inflammatory nature of COX-2 inhibitors, a potential role for them in increasing production of coated platelets seems counterintuitive. However, the facts that 5-LOX and COX-1 remain active during COX-2 inhibition and that the mediators responsible for modulating production of coated platelets are present at high concentrations make this a feasible hypothesis. One clinical observation supports the implication of COX-2 inhibitors in modulating coated platelet production. In a case report, Rashid et al. [77] described a woman taking rofecoxib (Vioxx) who developed an arterial thrombus during vascular access for an arteriogram. This patient had a coated platelet level of 63%. Eighteen months later, and with the patient no longer taking rofecoxib, the patient's coated-platelet value was 37% (normal range 25-40%).

Targeting 5-LOX and COX for Colon Cancer Prevention and Treatment

Targeting COX-2 for colon cancer has been well established in preclinical and clinical studies as discussed already. 5-LOX-inhibitors with anticarcinogenic properties have been evaluated predominately in cell lines [78]. Murine colon adenocarcinoma cell lines MAC16, MAC13, and MAC26 treated with the 5-LOX pathway inhibitors BWA4C, BWB70C, and zileuton—*N*-(1-benzo[*b*]-thien-2-yl)ethyl-*N*-hydroxyurea—at micromolar concentrations exhibited suppressed growth [79]. The same study further supported the *in vivo* inhibitory activities of these agents in male NMRI mice into which fragments of MAC26 or MAC16 colon tumors had been transplanted. Ye et al. [80] showed that dual inhibition of 5-LOX and

COX-2 by AA861 and celecoxib, respectively, suppressed colon cancer cell proliferation and tumor growth induced by cigarette smoke. Similarly, administration of zileuton and celecoxib in combination provided additive chemopreventive effects when compared with a single agent alone against dimethylbenzanthracene-induced oral cancers in hamsters [81].

5-LOX Inhibitors for CRC Prevention

Zileuton (Leutrol), a selective 5-LOX inhibitor of the *N*-hydroxyurea series developed by Abbott Laboratories, is the first orally active leukotriene inhibitor to show clinical efficacy in humans [82]. Zileuton is commonly used for the treatment of bronchial asthma. Several highly selective 5-LOX inhibitors are available; however, their anticarcinogenic properties are not fully established in preclinical studies. Zileuton was evaluated for its efficacy in heterotopic xenograft models using HT29 and LoVo human colon cancer cells. The 5-LOX inhibitor Rev-5901 and nordihydroguaiaretic acid—a nonspecific lipoxygenase (LOX) inhibitor—were studied for their effects on DNA synthesis via thymidine incorporation and cell counting. Inhibition of 5-LOX was shown to decrease DNA synthesis in a concentration- and time-dependent manner in the human colon cancer cells and to decrease tumor growth in the xenograft models. Rev-5901 also showed strong cytotoxic effects in various cancer cell lines and chemopreventive activity against colorectal adenocarcinoma xenografts. These studies support the conclusion that 5-LOX is an important target; they show that blockade of 5-LOX inhibits colon cancer cell proliferation both in vitro and in vivo and they suggest that 5-LOX inhibitors may provide a beneficial chemopreventive therapy in colon cancer [83]. Bolger et al. [84] recently developed (±)-4-acylnitroso cycloadducts with excellent inhibitory activity against 5-LOX. One compound was tested in vivo in an established colon cancer APC^{Min} mouse model and was shown to have antitumorigenic properties. Compound (±)-4a inhibited tumor formation by 62% and 73% relative to the control at 0.1 mg and 1.0 mg, respectively, in the APC^{Min} mice. Other 5-LOX inhibitors, such as AA861, have been shown to have similar effects in human colon cancer cells [85]. Another approach for targeting 5-LOX was shown by tissue-specific deletion of the 5-LOX gene, which profoundly attenuated polyp development in the APC^{Min} mouse model [86].

Modulation of 5-LOX and COX Activities by Naturally Occurring Agents

Curcumin, a major pigment in turmeric, has been identified as having anti-inflammatory and antioxidant properties [87]. It has been well studied for its anti-inflammatory roles in acute and chronic rat and mouse models. Its anti-inflammatory activity has been confirmed in clinical studies in patients with postoperative inflammation. It has been shown to reduce symptoms associated with rheumatoid arthritis, confirming its role in signaling pathways related to inflammation [87]. Inhibition of eicosanoid metabolism is the major mechanism by which curcumin exerts its anti-inflammatory action, with many articles showing COX/LOX inhibition by curcumin [87]. Dietary administration of curcumin (0.2%) in preclinical experiments decreased the levels of tumor phospholipase A₂ (50%) and phospholipase Cγ1 (40%), decreased formation of prostaglandins such as PGE₂, prostaglandin F_{2α}, prostaglandin D₂, 6-ketoprostaglandin F_{1α}, decreased the level of thromboxane B₂, and suppressed chemically induced colon cancers [88]. Various in vitro studies in CRC cell lines suggested that curcumin's antiproliferative effect is due to its effect on COX-2 expression. We reported that 0.2% curcumin administered in the diet to rats suppressed AOM-induced formation of 5-(*S*)-HETE, 8-(*S*)-hydroxyeicosatetraenoic acid [8-(*S*)-HETE], 12-(*S*)-hydroxyeicosatetraenoic acid [12-(*S*)-HETE], and 15-(*S*)-hydroxyeicosatetraenoic acid [15-(*S*)-HETE] by up to 53% in colonic mucosa and tumors [88]. In vitro results in macrophage Raw264.7 cells and in human CRC HT29 cells also suggest that curcumin effectively

inhibits 5-LOX activities [89]. These reports suggest that curcumin exhibits anti-inflammatory effects by inhibiting COX and LOX activities.

Phenylethyl caffeate (PEC) and phenylethyl-3-methyl caffeate (PEMC) are the phenolic constituents of honey that significantly inhibit proliferation of HT 29 human colon cancer cells [90]. We reported that 500 ppm of PEC and PEMC have potent inhibitory effects on AOM-induction of aberrant crypt foci (55% and 82%, respectively) associated with decreased AA metabolism [91]. PEC caused significantly decreased expression of LOX metabolites, 8-(*S*)-HETE and 12-(*S*)-HETE. PEC and PEMC (10, 50, and 100 μ M) suppressed in vitro 5-(*S*)-HETE, 12-(*S*)-HETE, and 15-(*S*)-HETE formation in colonic mucosa by up to 76% and 79%, respectively, in a dose-dependent manner [92]. Administration of PEMC at 750 ppm in the diet significantly inhibited the incidence and multiplicity of AOM-induced invasive adenocarcinomas (65.7%), noninvasive adenocarcinomas (40.3%), and total (invasive plus noninvasive) adenocarcinomas (47%) of the colon in F344 rats and it suppressed formation of 5-(*S*)-HETE, 8-(*S*)-HETE, 12-(*S*)-HETE, and 15-(*S*)-HETE in colonic mucosa and tumors by more than 30-60 % [92]. These results suggest that caffeic acid esters exhibit anti-inflammatory effects by suppressing LOX signaling pathways.

The ethanolic extracts of *Terminalia chebula* fruits (used to treat many diseases, such as diabetes, digestive diseases, colic pain, chronic cough, sore throat, and asthma) were tested for their ability to inhibit COX and 5-LOX. One of the fractionated compounds, chebulagic acid, showed potent dual inhibition against COX and 5-LOX and antiproliferative activity. The IC₅₀ values were 15 ± 0.28 , 0.92 ± 0.01 , and 2.1 ± 0.05 μ M for COX-1, COX-2, and 5-LOX, respectively, in human cancer cell lines, including HCT-15 and COLO-205 [93].

Development of Dual 5-LOX/COX Inhibitors

Recent studies demonstrating the gastrointestinal and cardiovascular toxicities of NSAIDs have prompted the search for novel approaches and agents with similar or higher efficacies. Targeting COX and 5-LOX pathways by using COX-2 and 5-LOX inhibitors simultaneously or by developing dual 5-LOX/COX inhibitors may provide better efficacy without unwanted cardiovascular and gastrointestinal side effects. Celecoxib and/or AA861 significantly reduced the stimulatory action of cigarette smoke extract on tumor size in a colon cancer xenograft model. The COX-2 inhibitor celecoxib alone caused 30% reduction of tumor growth, whereas the 5-LOX inhibitor AA861 caused 50% inhibition relative to the control group. The combination treatment of celecoxib and AA861 at their lower doses showed a more pronounced inhibitory action than treatment with either inhibitor alone [80].

Celecoxib and the 5-LOX inhibitor MK886 were studied for their effects on PGE₂ and cysteinyl leukotriene production and on tumor cell proliferation in the Caco-2 and HT29 human colon cancer cell lines. The selective inhibition of either 5-LOX or COX-2 alone resulted in activation of the other pathway in these cells. However, the combination treatment of celecoxib plus MK886 could prevent this activation and had additive effects on inhibition of tumor cell proliferation in comparison with treatment with either inhibitor alone. This study showed that inhibition of 5-LOX by MK886 could augment the antitumor activity of celecoxib in human CRC cells [94].

Licofelone (ML3000), a novel dual 5-LOX/COX inhibitor, suppresses 5-LOX and COX activities at equimolar concentrations (ratio approximately 1; IC₅₀ values approximately 0.20 μ M for both human 5-LOX and COX) [95]. Licofelone exhibits anti-inflammatory, analgesic, and antipyretic properties at a dose that causes no gastrointestinal damage [95, 96]. Preclinical and clinical (phase I and II) studies on licofelone suggest that this agent possesses several advantages when compared with general NSAIDs (indomethacin, aspirin,

naproxen) and COX-2-specific inhibitors (celecoxib, rofecoxib) in efficacy; and, more importantly, licofelone has no gastrointestinal side effects [96]. Recently, we have shown that licofelone suppresses small intestinal and colonic tumor formation in APC^{Min/+} mice in a dose-dependent manner with high efficacy and devoid of unwanted side effects [95]. We observed a dramatically higher efficacy of licofelone compared with NSAIDs (e.g., celecoxib and sulindac) and other agents studied previously in the APC^{Min/+} model [97]. Administration of licofelone to male F344 rats significantly inhibited the formation of AOM-induced aberrant colonic crypt foci (preneoplastic lesions) in a dose-dependent manner and caused a significant dose-dependent decrease in the COX-2 and 5-LOX activities [98]. On the basis of these published studies and our additional preliminary data, we suggest that licofelone will be an ideal agent to develop as a novel colon cancer chemopreventive agent.

Omega-3 fatty acids cannot be synthesized in the body and are obtained from diet. Foods rich in omega-3 fatty acids include walnuts, flaxseeds, rapeseeds, and fish. Eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA) are the key omega-3 polyunsaturated fatty acids (PUFAs) in fish oil. These PUFAs are powerful modulators of AA metabolism, and compared with AA, they are processed to different eicosanoids [99]. In the absence of PUFAs, AA is metabolized to the 2-series of prostaglandins and thromboxanes, most of which are proinflammatory, and the 4-series of leukotrienes. Prostaglandin H₂ is the immediate precursor of all 2-series prostaglandins and thromboxanes. COX and LOX are the important enzymes for conversion of AA to eicosanoids [97]. These AA-derived eicosanoids play a vital role in eliciting immune responses, in inducing inflammation, and in resolution of inflammation. PUFAs compete with desaturases and elongases and reduce the levels of AA-derived eicosanoids. The presence of omega-3 fatty acids inhibits the formation of the 2-series prostaglandins and increases production of 3-series prostaglandins and 5-series leukotrienes. PUFAs also lead to generation of resolvins and lipoxins, which are anti-inflammatory in function [99]. Hence, omega-3 fatty acids reduce COX-2 and 5-LOX activities and the production of proinflammatory eicosanoids, supporting their use as anti-inflammatory and antitumorigenic agents in colon cancer.

Resolvins are oxygenated metabolites of DHA and EPA. Low-dose aspirin leads to acetylation of COX-2 and to generation of 18-(*R*)-hydroxyeicosapentaenoic acid. This intermediate is further reduced to the hydroxyl compound by 5-LOX, and then undergoes a further reduction step to generate resolvin 2, and eventually, resolvin 1, which provides anti-inflammatory function. At local sites of inflammation, in the presence of PUFAs, aspirin treatment enhances the conversion of EPA and DHA to 18-(*R*)-oxygenated products, i.e., resolvins of the E and D series, which perform potent anti-inflammatory functions [99]. Resolvins have been shown to attenuate colonic mucosal inflammation in animals [100].

Lipoxin biosynthesis is through LOX–LOX interactions and transmembrane circuits. One of the methods of lipoxin generation is through low-dose aspirin generating 15-*epi*-lipoxin A4 or 15-*epi*-lipoxin B4 via 5-LOX. These products are called aspirin-triggered lipoxins; they possess potent anti-inflammatory functions similar to endogenous lipoxins. Lipoxins antagonize the functions of leukotrienes and have anti-inflammatory functions in colitis and an antiproliferative function in human colon cancer cell lines [99]. The presence of PUFAs will generate 15-*epi*-lipoxins in the presence of aspirin and COX-2. More detailed in-depth studies are necessary to understand the role of lipoxins in colon cancer prevention.

Conclusions

CRC is major health problem worldwide, with over 1.2 million new cases and nearly 600,000 deaths annually. Extensive studies of the pathobiological processes in CRC suggest

that inflammation is a major hallmark of colon tumor progression leading to adenocarcinoma. Among the various inflammatory mediators, arachidonate-derived eicosanoids, particularly COX-2 and 5-LOX metabolites, are well established as major contributors to colorectal tumor development. General NSAIDs and COX-2-selective inhibitors have proven to be highly efficient in the prevention of CRC at both preclinical and clinical levels; however, their frequent use in high doses and for long periods is associated with gastrointestinal ulcerations and increased risk of prothrombotic events in individuals at high risk of colon cancer. Recent advances in understanding the 5-LOX pathway and its contribution to the risk of CRC thrombosis support the targeting of this pathway along with COX-2 in cancer prevention and therapy. Targeting 5-LOX and COX-2 can be achieved by highly selective inhibitor combinations or by development of dual 5-LOX/COX inhibitors such as licoferone. Preclinical rodent efficacy studies suggest that targeting both 5-LOX and COX-2 is more efficient in suppressing colonic tumors than targeting COX-2 or 5-LOX alone. This finding need to be validated further in human clinical trials. In addition to synthetic drugs targeting 5-LOX/COX2, several naturally occurring agents, such as curcumin, PEC, and omega-3 fatty acids have been shown to suppress 5-LOX and COX-2 expression and to alter formation of protumorigenic metabolites. Overall, the roles of 5-LOX and COX-2 in colon tumor development are becoming well established, and targeting both of these pathways is an important strategy for CRC prevention and treatment.

Acknowledgments

The authors are supported by a grant from the National Cancer Institute.

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Fig. 1.

Targeting 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2) for colorectal cancer prevention and treatment. Arachidonic acid is produced from membrane phospholipids as part of a major pathway involved in pain and inflammation. Arachidonic acid is further metabolized by lipoxygenase and cyclooxygenase pathways. Among lipoxygenases, 5-LOXs produce leukotrienes, which play major roles in inflammation and gastrointestinal (GI) damage and contribute to protumorigenic conditions. One of the leukotrienes is converted to lipoxin A₄ through 15-lipoxygenase and helps in resolving inflammatory conditions; it exhibits antitumorigenic activity. The cyclooxygenase pathway produces prostaglandin H₂ (PGH₂), which serves as a substrate for conversion to various other prostaglandins. Many prostaglandins and thromboxanes have proinflammatory and prothrombotic effects, leading to increased risk of potentially fatal cardiovascular events. COX cyclooxygenase, 5-HETE 5-(S)-hydroxyeicosatetraenoic acid, 5-HPETE 5-(S)-hydroperoxyeicosatetraenoic acid, LTA₄ leukotriene A₄, LTB₄ leukotriene B₄, LTC₄ leukotriene C₄, LXA₄ lipoxin A₄, PGD₂ prostaglandin D₂, PGE₂ prostaglandin E₂, PGF₂ prostaglandin F₂, PGI₂ prostacyclin, TXA₂ thromboxane A₂