

Chapter 2

The Role of Inflammation in Colon Cancer

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Abstract Colorectal cancer (CRC) is the one of the leading causes of cancer-related deaths in the world. CRC is responsible for more than 600,000 deaths annually and incidence rates are increasing in most of the developing countries. Epidemiological and laboratory investigations suggest that environmental factors such as western style dietary habits, tobacco-smoking, and lack of physical activities are considered as risks for CRC. Molecular pathobiology of CRC implicates pro-inflammatory conditions to promote the tumor malignant progression, invasion, and metastasis. It is well known that patients with inflammatory bowel disease are at higher risk of CRC. Many evidences exist reiterating the link between Inflammation and CRC. Inflammation involves interaction between various immune cells, inflammatory cells, chemokines, cytokines, and pro-inflammatory mediators, such as cyclooxygenase (COX) and lipoxygenase (LOX) pathways, which may lead to signaling towards, tumor cell proliferation, growth, and invasion. Thus, this review will focus on mechanisms by which pro-inflammatory mediators and reactive oxygen/nitrogen species play a role in promoting CRC. Based on these mechanisms, various preventive strategies, involving anti-inflammatory agents, such as COX inhibitors, COX-LOX inhibitors, iNOS inhibitors, natural supplements/agents, and synthetic agents, that blocks the inflammatory pathways and suppress CRC are discussed in this review.

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Abbreviations

CRC	Colorectal cancer
CAC	Colitis-associated cancer
IBD	Inflammatory bowel disease
NSAIDs	Non-steroidal anti-inflammatory drugs
NK	Natural killer cells
DC	Dendritic cells
ACF	Aberrant crypt foci
T reg	T regulatory cells
5-ASA	5-aminosalicylic acid
MCP-1	Monocytes chemo attractant protein 1
PGE ₂	Prostaglandin E ₂
IL-8	Interleukin-8
IL-6	Interleukin-6
IL-10	Interleukin 10
TNF- α	Tumor necrosis factor- α
COX-2	Cyclooxygenase-2
PGI ₂	Prostaglandin I ₂
PGD ₂	Prostaglandin D ₂
LT	Leukotriene
HPETE	Hydroperoxyeicosatetraenoic acid
EETs	Epoxy-eicosatrienoic acids
EPA	Eicosapentaenoic acid
DHA	Decosahexaenoic acid
PUFAs	Polyunsaturated fatty acids (PUFAs)
LX	Lipoxins
RVs	Resolvins
AOM	Azoxymethane
NO	Nitric oxide
NF- κ B	Nuclear factor- κ B
MMP	Matrix metalloproteinase
PI3K	Phosphatidylinositol 3-kinase
mPGES	Microsomal prostaglandin E synthase
VEGF	Vascular endothelial growth factor
FLAP	Five lox activating protein
DP1	PGD ₂ receptor
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
NO	Nitric oxide
iNOS	Inducible nitric oxide synthase
nNOS	Neuronal nitric oxide synthase
eNOS	Endothelial nitric oxide synthase
APC	Adenomatous polyposis coli
LPS	Lipopolysaccharide

IL-1 β	Interleukin-1 β
AA	Arachidonic acid
NO-NSAID	NO-releasing NSAID
IL-4	Interleukin 4
COXibs	COX-2-specific inhibitors
FAP	Familial adenomatous polyposis
L-NAME	<i>L</i> -nitro arginine methyl ester
Se-PBIT	Selenium [<i>S,S'</i> -1,4-phenylene <i>bis</i> (1,2-ethanediyl) <i>bis</i> -isothioureia]
GI	Gastrointestinal
MIP	Macrophage inflammatory protein
MCP	Monocytes chemo attractant protein
ABC	ATP-binding cassette
DMH	Dimethyl hydrazine
MDFs	Mucin depleted foci
DSS	Dextran sulfate sodium
EPA-FFA	Eicosapentaenoic acid-free fatty acid
ONA	Oleanolic acid
OT	18 α -olean-12-ene-3 β -23,28-triol
18 <i>R</i> -RvE1	5,12,18 <i>R</i> -trihydroxy-EPA
LXA ₄	lipoxins A ₄
ABC	ATP-binding cassette

2.1 Colorectal Cancer: A Major Health Problem

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in the United States (US). Early diagnosis, though, often can lead to a complete cure. Each year, worldwide more than 1.2 million cases are diagnosed with about 600,000 deaths. CRC is the third most common cancer diagnosed in both men and women in the US and the fourth most common cause of cancer mortality worldwide (Tenesa and Dunlop 2009). It is the second most common cause of cancer deaths in the US. Overall, the lifetime risk of developing CRC is ~6 %. As per American Cancer Society statistics, it is expected to cause about 50,830 deaths during 2013 (ACS). Most of the CRC cases are sporadic and about 25 % are linked to genetic disorders. The majority of CRC cases are linked to environmental factors, including diet, exercise, weight, food borne mutagens, intestinal commensals, and chronic intestinal inflammation, which precedes tumor development.

2.2 Inflammatory Bowel Disease as Risk Factor for Colorectal Cancer

Inflammatory bowel disease (IBD) may lead to colitis-associated cancer (CAC), which is a usually difficult-to-treat cancer having high mortality (Feagins et al. 2009). It is reported that more than 20 % of IBD patients develop cancer and 50 % of these will

die of colon cancer (Lakatos and Lakotos 2008). These patients are reported to have increased inflammatory infiltration and increased expression of inflammatory genes (Atreya and Neurath 2008; Atreya et al. 2008; Waldner and Neurath 2008; Clevers 2004). A higher risk for colon cancer is observed in IBD patients who have a family history of CRC (Askling et al. 2001). This increased risk suggests an overlap of signaling pathways and mechanisms that drive cancer development in CAC and CRC. Anti-inflammatory therapy has been reported to reduce the risk or prevent CRC and colitis-related CRC in several observational studies. Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to reduce colorectal neoplasia by 40–50 % (Thun et al. 1991; Smalley and Dubois 1997) and also have been reported to reduce CRC mortality odds by 49 % in a population of US military veterans with IBD (Bansal and Sonnenberg 1996). A recent meta-analysis of 9 observational studies reported that use of 5-aminosalicylic acid (5-ASA), mesalamine reduced the odds of colitis-related CRC by 49 % (Velayos et al. 2006). It is noteworthy that anti-inflammatory drugs such as 5-aminosalicylate-based compounds have remained in the mainstream for the treatment of IBD patients for >50 years. The findings in the human studies confirm observations in animal models, which show that NSAIDs reduce the occurrence of intestinal neoplasia. More than 90 % of 110 preclinical animal studies examining the effects of NSAIDs on tumorigenesis reported an anti-neoplastic effect (Hawk and Levin 2005). The large volume of compelling data on the use of anti-inflammatory agents/NSAIDs to reduce the risk of CRC suggests a potential role of inflammation in CRC.

2.3 Inflammation in CRC

Inflammation is driven by the accumulation of various immune and inflammatory cells and soluble inflammatory mediators, such as cytokines, chemokines, growth factors, lipid molecules, reactive oxygen, and nitrogen species. The interaction between these immune and inflammatory cells and cytokines leads to generation of autocrine and paracrine signals that foster tumor cell progression, growth, and metastases. A clear link exists between inflammation and CRC. Even CRC that is linked to genetic mutations shows a contribution from inflammation to tumor development, as shown by the decreased CRC mortality with regular use of NSAIDs. These data strongly support a pro-tumorigenic role of inflammation in colon cancer. Various factors can influence the initiation of inflammation and establishment of CRC.

2.4 Role of Immune and Inflammatory Cells in CRC

Pathological analysis of CRC shows infiltration with various types of cells that function in innate immunity, such as neutrophils, mast cells, natural killer (NK) cells, dendritic cells (DC), and tumor-associated macrophages (Atreya and Neurath 2008).

These cells help in anti-tumor immune responses by suppressing tumor growth and angiogenesis. They also help to recruit and interact with other cells involved in adaptive immune responses. Collectively, these responses lead to a balancing of immune surveillance with tumor-promoting inflammatory functions. Immune surveillance helps in early detection of aberrant crypt foci (ACF) and elimination of aberrant cells, which may progress into adenomas and adenocarcinomas in CRC. However, when a chronic inflammation persists, it creates an environment that out-competes immune surveillance mechanisms and creates a microenvironment that favors inhibition of anti-tumor immune responses and leads to formation of tolerogenic DCs and infiltration of T regulatory cells (T reg), which help in establishment of tumor cell growth. T reg infiltration is associated with bad prognosis (Erdman et al. 2005; Dunn et al. 2004). Thus, it is necessary to design drugs and standardize doses that will inhibit only tumor-promoting immune responses and will spare tumor-inhibiting responses.

2.5 Resolution of Inflammation and Pro-Inflammatory Mediators in CRC

Macrophages accumulate at the site of inflammation or injury and are activated by the cytokines interleukin-10 (IL-10), tumor necrosis factor- α (TNF- α), and monocytes chemoattractant protein (MCP-1). Neutrophils follow for resolution of inflammation. Eventually, fibroblasts play a role in tissue repair by secreting pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and prostaglandin E₂ (PGE₂), which will help in the neutrophil response. Epithelial cells and stromal cells together help in repairing/healing the wound. Resolution of inflammation by recruitment of neutrophils can lead to complete remission of inflammation and stop the aberrant proliferation, which can extend into tumor growth. However, if this active process of resolution of inflammation is impaired, the on-going tissue repair eventually may lead to chronic inflammation, which predisposes to cancer. Cyclooxygenase (COX) and lipoxygenase (LOX) pathways and persisting inflammatory cells are involved in generating pro-inflammatory lipid mediators and gene responses, creating a favorable microenvironment that eventually can lead to tumor cell growth, proliferation, and metastases.

2.6 Role of Inflammatory Bioactive Arachidonic Acid Lipid Metabolites in CRC

Arachidonic acid (AA) is an omega-6 polyunsaturated fatty acid (PUFA) present in the phospholipids of cell membranes. It acts as a precursor for production of various eicosanoids usually generated by three enzymes: COX, LOX, and cytochrome p450. The metabolites formed by action of COX and LOX are prostaglandin I₂

(PGI₂), prostaglandin D₂ (PGD₂), PGE₂ and thromboxane A₄ and Leukotrienes (LT)-A₄, C₄, D₄ and B₄, respectively. The LOX metabolites involve hydroperoxy-eicosatetraenoic acids (HPETE) such as 5-HPETE, 12-HPETE, and 15-HPETE. The metabolites of P450 are epoxy-eicosatrienoic acids (EETs) resulting in four regioisomeric EETs (5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET). The other metabolites that play a role during inflammatory processes are omega-3FAs [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] derived from PUFAs. The other important bioactive molecules derived from these intermediates are lipoxins (LX) and resolvins (RVs). Unlike some of the COX and LOX metabolites, these bioactive molecules display potent anti-inflammatory, immunoregulatory, pro-resolving and anti-tumorigenic properties.

2.6.1 Role of Inflammatory Lipid Molecules Derived from the COX-2 Pathway in CRC

COX-2 is the inducible COX gene that mediates prostaglandin synthesis and pro-inflammatory functions. The expression of COX-2 is elevated in 50 % of adenomas and in 85 % of adenocarcinomas. In human intestinal tumors, COX-2 is expressed in epithelial and stromal cells; it usually is induced by interleukin 1 β (IL-1 β) and TNF- α . Over-expression of COX-2 increased azoxymethane (AOM)-induced tumor formation (Al-Salihi et al. 2009); and COX-2 deficiency significantly diminished tumorigenesis in mouse models of colon cancer (Chulada et al. 2000a, b; Oshima et al. 1996a, b), confirming a role for COX-2 in tumorigenesis. The pro-inflammatory and pro-tumorigenic effects of COX-2 are mediated by its major end product, PGE₂, which stimulates tumor cell proliferation/growth, angiogenesis, and survival and inhibits apoptosis in CRC (Wang and Dubois 2006; Castellone et al. 2006). PGE₂ activates a number of oncogenic signaling pathways, including β -catenin/transcription factors (TCF), Ras, and the phosphatidylinositol 3-kinase (PI3K) pathways. The generation of microsomal prostaglandin E synthase (mPGES-1)-deficient mice has revealed a dominant role of this enzyme in PGE₂ generation relevant to promotion of inflammation (Trebino et al. 2003). The mPGES-1-derived-PGE₂ exhibits similar inflammatory responses during tumor growth. mPGES-1 deficiency was linked to reduced vascular endothelial growth factor (VEGF). Together, these findings show that deletion or inhibition of mPGES-1 markedly reduces inflammatory responses in mouse models and eventually may lead to inhibition of tumor cell proliferation.

PGD₂, another important metabolite of COX-2, appears to be a negative regulator of tumorigenesis; it has been demonstrated to possess anti-tumor properties (Murata et al. 2008). It is produced locally by inflammatory cells at sites of inflammation; and its receptor (DP1) also is expressed highly in tumor endothelial cells. The DP1 receptor is expressed on DCs that play a key role in initiating an adaptive immune response to foreign antigens (Hammad et al. 2003). These studies suggest that different COX-2-derived prostaglandins have opposing effects on

inflammation and tumor cell proliferation and that selective modulation of these prostaglandins may prevent tumor growth in CRC.

2.6.2 Role of Lipid Molecules Derived from the LOX Pathway in Inflammation and CRC

Among the LOX pathways, 5-LOX and 12-LOX pathways are closely related to inflammation and carcinogenesis; however, metabolites from another LOX pathway, 15-LOX are linked positively and shown to inhibit inflammation and carcinogenesis. A number of reports suggest the involvement of 5-LOX in early stages of CRC (Qiao et al. 1995; Bortuzzo et al. 1996; Avis et al. 2001; Ding et al. 2003; Tong et al. 2005). Hong et al. (1999) reported high expression of 5-LOX and 5-LOX-activating protein in cancer cell lines. High expression of 5-LOX and its receptors was observed in CRC patients showing poor prognosis (Ohd et al. 2003). Accumulation of 5-HETE and LT upon activation of 5-LOX resulted in cancer cell proliferation (Ding et al. 1999). COX and LOX pathways are both linked in such a way that disturbance in one pathway may lead to over-expression of the other pathway; thus, balanced inhibition of these two pathways is favorable for inhibiting CRC (Byrum et al. 1997; Griffiths et al. 1997; Goulet et al. 1994). Many studies have suggested that removal of 5-LOX and 5-LOX-activating protein (FLAP) results in increased expression of COX metabolites (Byrum et al. 1997; Goulet et al. 1994). These studies provide evidence for an important role of 5-LOX in CRC and suggest the potential for chemoprevention and treatment for CRC. Thus, targeting both COX-2 and 5-LOX pathways together and increasing production of LX and RVs is a better approach for prevention/treatment of CRC.

2.6.3 Role of Reactive Oxygen and Nitrogen Species in Inflammation and CRC

Inflammation also is associated with generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Free radicals are known to be involved in carcinogenesis (Goldstein and Witz 1990; Cerutti 1985). Inflammatory phagocytic cells make ROS. $O_2^{\cdot -}$ is the initial ROS and undergoes sequential metabolic changes that generate other species (i.e., OH, OCI^- , and H_2O_2). Usually, these reactive species lead to mutations in DNA that may be mutagenic and involved in the etiology of cancer (Babbs 1990). A significant increased expression in ROS was reported by Haklar et al. (2001) in patient colon tumors.

The literature in this area generally is consistent with the view that the enhanced production of ROS and bioavailability of nitric oxide (NO) that accompany an inflammatory response play pivotal roles in mediating formation of microvessels during tumor growth. Activated inflammatory cells produce ROS and reactive nitrogen

intermediates that can induce DNA damage and mutation in adjacent epithelial cells. These changes can stimulate ROS production within the epithelial cells may cause epigenetic silencing of tumor suppressor genes (Meira et al. 2008; Westbrook et al. 2009). The discovery of NO as a product of immune system cells has implicated this chemical in the mechanism of carcinogenesis (Tamir and Tannenbaums 1996). Produced NO can interact with $O_2^{\cdot-}$ resulting in the propagation of the highly reactive species peroxynitrite (Oshima and Bartsch 1994). Peroxynitrite, which is formed from the reaction between $O_2^{\cdot-}$ and NO, reacts with all classes of biomolecules and thereby is thought to be involved in many pathologic phenomena (Bartosz 1996). NO and peroxynitrite concentrations were reported to be increased in cancerous samples (Haklar et al. 2001). NO is produced by three isoforms of nitric oxide synthase (NOS) [neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS), and inducible NOS (iNOS)]. nNOS and eNOS are constitutive NOS isoforms, whereas iNOS is induced upon exposure to inflammatory stimulation. iNOS is expressed in many cells: extravascular resident leukocytes (macrophages), intravascular and/or infiltrating leukocytes (neutrophils and monocytes), endothelium, and parenchymal cells, including intestinal epithelium. Its production is stimulated by lipopolysaccharide (LPS), TNF- α , or interleukin-1 β (IL-1 β). The role of NO in colon cancer is controversial. Increased production of NO for a limited time is considered to produce positive results in inhibiting CRC, whereas chronic and continuous production of NO produced by iNOS is implicated in neoplastic transformation, a very crucial step during carcinogenesis. Studies with iNOS knockout mice suggested a positive role for iNOS in inducing polyps in adenomatous polyposis coli (APC) min/+ mice (Hofseth et al. 2003; Crowell et al. 2003; Ahn and Oshima 2001; Nam et al. 2004). High expression of iNOS in CRC xenografts suggested an inhibitory role for iNOS in tumor growth (Xu et al. 2002). In various preclinical studies in animal models, we noted that iNOS inhibitors show promise for inhibiting CRC (Rao et al. 1999, 2002). In summary, both increased expression and decreased expression of NO is observed to have beneficial effects on CRC. Carefully designed, detailed studies to understand the role of NO during inflammation are necessary in order to understand how to modulate its effects in CRC. Interactions between NO and COX-2 are well documented, and combinations of iNOS inhibitors and COX-2 inhibitors have provided inhibition of invasive adenocarcinomas in animal models of colon cancer (Janakiram and Rao 2012).

2.7 Anti-inflammatory Agents in Prevention of CRC

Since it is evident that inflammation is a significant contributor to CRC, anti-inflammatory agents, both from synthetic and natural origin, have gained importance for use in prevention and treatment of CRC. As mentioned previously, NSAIDs are the main anti-inflammatory agents shown to possess anti-tumorigenic properties. They function by inhibiting AA-related pathways and by enhancing immune responses against tumor development. iNOS inhibitors also have gained importance as anti-inflammatory agents in CRC and in other cancers. CRC is associated with lower consumption of fruits and vegetables and greater consumptions of fatty foods implicated

in causing CRC, thus natural constituents in these and other foods may contribute to reduce cancer risk or prevention. Here, we discuss various synthetic and natural bio-active compounds that can activate or deactivate signaling cascades implicated during tumor development and that may exhibit chemopreventive properties.

2.7.1 Synthetic Anti-Inflammatory Agents for Prevention of CRC

Preclinical and clinical evidences suggest the presence of high levels of prostaglandins, such as PGE₂ as mentioned earlier, which affect tumor cell proliferation by suppressing immune responses (Marnett 1992; Smith 1992). Hence, it is reasonable to use NSAIDs that can suppress the synthesis of these prostaglandins by inhibiting COX enzymes may in turn suppress tumor development and growth in colon.

Epidemiological studies, intervention trials, and animal studies have provided compelling data for inhibition of colorectal carcinogenesis by aspirin and other NSAIDs (Giovannuci 1999; Brown and Dubois 2005). The first epidemiological report suggested use of aspirin to decrease risk for CRC (Kune et al. 1988). Most of the subsequent case-control studies and prospective studies supported these results (Thun et al. 1991; Freedman et al. 1998; La Vecchia et al. 1977; Muscat et al. 1994; Peleg et al. 1994; Suh et al. 1993; Giovannucci et al. 1994; Schreinemachers and Everson 1994; Chan et al. 2005). The relative risks were very consistent in reducing the risk to 50 % in aspirin users compared with non-aspirin users. Studies on precursors of CRC such as adenomatous polyps have shown similarly decreased risks (Suh et al. 1993; Greenberg et al. 1993; Logan et al. 1993; Martinez et al. 1995). Whereas, the risk reduction of CRC is linked to the dose intake and also the duration of aspirin use which is explored in a subset of studies. Across-study comparisons indicate a dose-response relationship between aspirin and CRC or other cancer types (Harris et al. 2005). A greatest risk reduction was seen among women who took more than two aspirin tablets daily reported by the Nurses' Health Study support a strong dose-response relationship with colon cancer (Chan et al. 2005). Ten years of consistent aspirin use seems to be having reduced risks of CRC which is evidenced and seems consistent (Chan et al. 2005). Further, the role of NSAIDs/aspirin use is substantially strengthened in secondary prevention for reduction of metachronous lesions among patients with primary colorectal adenomas or CRC by two randomized controlled trials. In this trial, aspirin had a modest effect on patients with previous adenomas in reducing the risk of developing new adenomas or cancer that differed by dose. In this study, a lower dose (81 mg/day) showed better response of 19 % reduced risk of adenomas than a higher dose (325 mg/day) (Sandler et al. 2003; Baron et al. 2003). Aspirin use as a chemopreventive agent is strongly supported by these trails against colorectal carcinogenesis among individuals with a known increased risk as a result of previous disease.

We and others have previously shown that several COX inhibitors, such as indomethacin, piroxicam, aspirin, ibuprofen, and sulindac suppress colon carcinogenesis in AOM-induced F344 rats (Reddy et al. 1993, 1987; Metzger et al. 1984; Narisawa

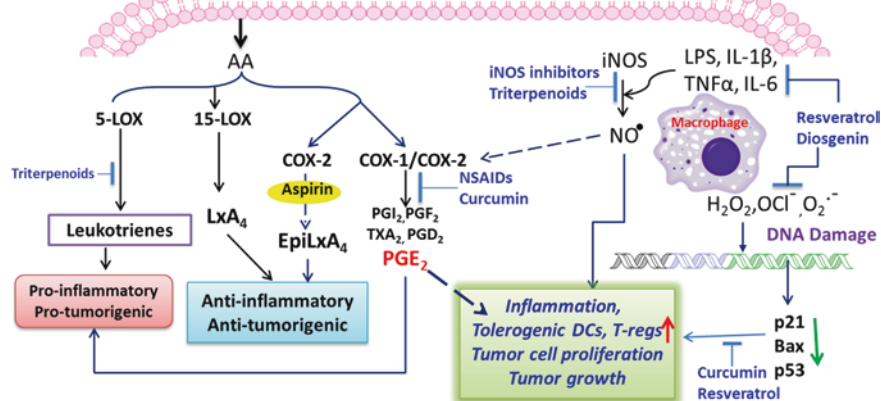


Fig. 2.1 The figure depicts the various pathways observed which initiates inflammation and tumor cell proliferation. Arachidonic acid metabolism leads to formation of both pro-inflammatory and anti-inflammatory metabolites. 5-LOX pathway leads to formation of leukotrienes which are known for their pro-inflammatory and pro-tumorigenic role. Triterpenoids are reported to show inhibitory effects on formation of leukotrienes. COX-2 in the presence of aspirin will lead to formation of epilipoxins (*epiLXA₄*), which are anti-inflammatory and anti-tumorigenic in functions. Naturally 5-LOX pathway leads to formation of lipoxins, which show similar functions as that of *epiLXA₄*. COX-1 and COX-2 pathway leads to the formation of eicosanoids, PGI₂, PGF₂, TXA₂, PGD₂, and PGE₂. PGE₂ has been found to play a vital role during inflammation, development of Tregs, formation of tolerogenic DCs, tumor cell proliferation, and growth. NSAIDs and natural agent like curcumin are reported to have inhibitory effects on the formation of eicosanoids. LPS, IL-1β, and TNF-α are known to be involved in formation of nitric oxide (NO), and IL-6 is a known inflammatory cytokine involved during tumorigenesis. NO formed can initiate the inflammation and tumor formation by itself or by interacting COX-2 pathway. iNOS inhibitors and triterpenoids are shown to inhibit NO formation, and resveratrol and diosgenin inhibit pro-inflammatory cytokines. The free radical formation by macrophages which can cause DNA damage and eventually tumor cell proliferation by down-regulating p21, p53, and BAX are observed. Curcumin and resveratrol are reported to restore p21, p53, and p53 and inhibit tumor cell proliferation

et al. 1993; Pollard and Luckert 1984; Moorghen et al. 1988). Indomethacin was reported to inhibit tumor growth in chemically induced large-bowel tumors in rats (Kudo et al. 1980). Similar results were observed in other preclinical studies (Pollard and Luckert 1980, 1981; Narisawa et al. 1981). Due to GI toxicities of indomethacin, we developed and tested a potentially less toxic derivative, NO-indomethacin, in AOM-induced carcinoma models. Nitric oxide-releasing non-steroidal anti-inflammatory drugs (NO-NSAID) are promising chemoprevention agents; unlike conventional NSAIDs, they seem to be free of appreciable adverse effects, while they retain the beneficial activities of their parent compounds. NO-indomethacin significantly suppressed AOM-induced tumor multiplicity and incidence in F344 rats (Rao et al. 2006). Its activity is related to suppression of COX, iNOS, and β-catenin levels (Fig. 2.1).

Rigau et al. (1991) have demonstrated that colon mucosal samples from patients on long-term sulindac therapy have a reduced PG-biosynthetic capacity. In a randomized, placebo-controlled, double-blind crossover study in patients with familial adenomatous polyposis (FAP), administration of sulindac at a dose of 300 mg/day for 6–12 months caused disappearance of all polyps (Laybayle et al. 1991). Most of the clinical trials with FAP patients on long-term treatment with sulindac reported a reduction in the number and size of adenomas (Belliveau and Graham 1984; Waddel et al. 1989; Laybayle et al. 1991; Spagnesi et al. 1994; Winde et al. 1993; Giardello et al. 1993). Dietary administration of sulindac inhibited dimethyl hydrazine (DMH)-induced colon tumor incidence and multiplicity in mice (Moorghen et al. 1998; Skinner et al. 1991). In these experiments, sulindac was administered along with DMH throughout the study; however, administration of sulindac to mice seventeen weeks after DMH administration showed no reduction in colon tumor growth or development. Oral administration of sulindac (10 mg/kg) twice daily inhibited DMH-induced primary colon tumor development and growth in rats. Ahnen et al. (1994) showed that dietary administration of sulindac and its metabolite sulindac sulfone significantly inhibited AOM-induced colon carcinogenesis in F344 rats. We found that sulindac was effective at both initiation and postinitiation stages of colon tumor formation in F344 rats (Rao et al. 1995). This study suggested that its inhibitory function may be due to its modulatory effects on AA metabolism. In another study by Suh et al. (2011), the NSAIDs sulindac and naproxen, individually and in combination with atorvastatin, caused significant reduction in AOM-induced colon tumors in F344 rats. The NSAID-fed animals showed reduction in inflammatory markers iNOS and COX-2 as well as in phospho-p65 and in the pro-inflammatory cytokines TNF- α , IL-1 β , and interleukin 4 (IL-4). Hence, use of NSAIDs in combination with statins was suggested for retaining efficacy with less/no GI toxicity.

The concern over gastric toxicity associated with aspirin use led to efforts to develop COX-2-specific inhibitors (COXibs such as rofecoxib, celecoxib) (Gupta and Dubois 2001). Available literature provides strong evidence for a role of COX-2 in inflammation and carcinogenesis. Several studies using COX-2 knock-out or disrupted genes in mouse models of FAP or in chemically induced colon carcinogenesis in rats indicated that COX-2 selective inhibitors, such as rofecoxib and celecoxib, inhibit formation of intestinal adenomas (Dannenbergh et al. 2005; Rao and Reddy 2004; Oshima et al. 1996a, b, 2001; Chulada et al. 2000a, b; Jacoby et al. 2000; Boolbol et al. 1996; Mahmoud et al. 1998; Kawamori et al. 1998; Reddy and Rao 2002). In a clinical trial, FAP patients treated twice daily with 400 or 200 mg celecoxib had 31 and 12 % reduction, respectively, in polyp number (Arber et al. 2006). In this clinical trial, celecoxib, at a dose of 400 mg daily, reduced advanced adenoma formation in the colon by almost 50 % compared with the placebo through a 3-year treatment period (Arber et al. 2006). Although introduction of COXibs was successful in reducing GI toxicity, these drugs were associated with cardiovascular toxicity due to high selectivity toward COX-2 (Smith et al. 2000; Silverstein et al. 2000; Laine et al. 2003; Bresalier et al. 2005; Nussmeier et al. 2005; Solomon et al. 2005). An initial study indicated

possible increases in the incidence of myocardial infarction with use of COXibs (Bombardier et al. 2000). No randomized controlled trials specifically to address the issue of cardiovascular toxicity were conducted; but trials were initiated to test the efficacy of COXibs in the prevention of metachronous colonic polyps (Bresalier et al. 2005; Solomon et al. 2005) and the management of postoperative pain (Nussmeier et al. 2005). The above-mentioned trials suggested that patients using these COX-2 inhibitors were showing cardiovascular events. These observations led to temporary withdrawal of COXibs from the US market in 2004. The findings suggest that this cardiovascular toxicity is specific to this class of drugs; but aspirin and other non-specific COX-2 inhibitors still have potential for chemoprevention of CRC.

In February 2005, the Food and Drug Administration (FDA) Advisory Committee meeting recommended that COXibs remain on the market, but with warnings added to labels (Alberts et al. 2005). The committee agreed that since celecoxib is the least likely to be associated with adverse cardiovascular events, it is the most appropriate COXib to study for the prevention and treatment of cancer. Complicating the risk—benefit evaluation are individual differences in both cancer risk and sensitivity to toxic events. The development of very low non-toxic doses of COXibs or COX and LOX-inhibiting regimens in combination with other agents continues. Licofelone (ML3000) is the first member of a new dual COX/5-LOX inhibitor class and currently is under evaluation as a treatment for osteoarthritis. A multicenter study explored the effects of licofelone in comparison with naproxen as a disease-modifying agent and showed beneficial effects on cartilage. Although phase III trials have been completed successfully, no dates for regulatory submission have been given for this drug. Its safety profile shows fewer GI events than NSAIDs and selective COX-2 inhibitors (Martel-Pelletier et al. 2003; Cicero et al. 2005; Moreau et al. 2005; Bias et al. 2004). We tested licofelone in APC^{Min/+} mice and found it to possess potential chemopreventive properties (Mohammed et al. 2011). The efficacy achieved with licofelone was comparable to or more effective than several NSAIDs and the COX-2-selective inhibitors celecoxib and rofecoxib (Swamy et al. 2006; Jacoby et al. 1996; Rao and Reddy 2004; Rao et al. 2000; Orner et al. 2003). This result suggests that a balanced inhibition of COX and LOX pathways is a better approach to obtain diminished side effects with high efficacy. The beneficial effects of NSAIDs in chemoprevention of CRC suggest that inflammatory mechanisms are playing a vital role in tumor development, with strongest for colorectal cancer. Future work to understand the molecular mechanisms still is needed to establish the chemopreventive potential of NSAIDs for use as a preventive for and treatment of CRC.

2.7.2 Role of iNOS Inhibitors in Prevention of CRC

High NOS activity and high levels of NO are observed in AOM-induced colonic tumors in rats (Rao et al. 1999, 2002), in Crohn's disease (Rachmilewitz et al. 1995)

and in ulcerative colitis (Colon et al. 2000). Over-expression of NO was observed in preneoplastic colon lesions and also in human colon adenocarcinomas (Hao et al. 2001; Yagihashi et al. 2000; Lagares-Garcia et al. 2001; Szaleczky et al. 2000). High iNOS levels were observed in colons of animals fed a high-fat diet, suggesting a role of high-fat diets in inducing inflammatory conditions and CRC in humans (Wan et al. 2000). Collectively, these studies support a positive role of iNOS in inducing CRC and use of iNOS-inhibiting agents for suppressing the iNOS activity and its tumorigenic effects (Fig. 2.1).

S,S-1,4-phenylene-*bis*(1,2-ethanediyl)-*bis*-isothioureia, PBIT a selective iNOS inhibitor, caused suppression of ACF development in rats by reducing protein levels of j; and iNOS in colonic mucosa (Rao et al. 1999). Kawamori et al. (2000) reported similar results with *L*-nitro arginine methyl ester (L-NAME), an *L*-arginine inhibitor on the development of ACF induced by AOM in rats. Animals that received 100 ppm of L-NAME for 11 weeks showed 32 % inhibition of ACF multiplicity. To increase the potency of PBIT with lower concentrations, a isosteric analog of PBIT, selenium [*S,S'*-1,4-phenylene-*bis*(1,2-ethanediyl) *bis*-isothioureia] (Se-PBIT) was developed and tested recently, in colon cancer animal model. We reported chemopreventive properties of Se-PBIT on ACFs induced by AOM in rats (Janakiram et al. 2013). We have studied extensively the role of iNOS inhibitors in colon carcinogenesis (Rao et al. 2002; Rao 2004). We tested iNOS-selective inhibitors individually and in combination with COX inhibitors and found that low-dose combinations of the COX-2 inhibitor celecoxib and the iNOS inhibitor SC-51 inhibited AOM-induced crypt formation in rats (Rao 2004). L-NAME and iNOS-specific inhibitors have been reported to have inhibitory effects on formation of adenomas, adenocarcinomas (Kawamori et al. 2000; Schleiffer et al. 2000), and adenomatous polyps (Ahn and Ohshima 2001). NO signaling cascades also are involved in the migration of tumor cells. More detailed studies into role of NO at different doses and during different stages of tumor development are necessary for design of better iNOS inhibitors for prevention and treatment of CRC.

2.7.3 Natural Anti-Inflammatory Agents for Prevention of CRC

Epidemiologic evidence supports the benefit of changes in dietary and exercise patterns for CRC prevention. Among well-known dietary agents, curcumin has been valued for more than 5,000 years for its medicinal properties and for its warm, peppery flavor. Curcumin is one of the curcuminoids of turmeric. Curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. It is reported to interact with inflammatory processes by down-regulating COX-2, 5-LOX, iNOS and also production of inflammatory cytokines such as TNF- α , IL-1, -2, -6, -8 and -12, and also macrophage inhibitory protein (MIP), monocytes chemoattractant protein (MCP), and matrix metalloproteinases (MMPs) (Goel et al. 2008; Abe et al.

1999) (Fig. 2.1). Curcumin was found to be effective in reducing colitis induced by 1,4,6-trinitrobenzene sulfonic acid. Ukil et al. (2003) reported reduced levels of NO and O₂ radicals and suppression of NF- κ B activation in curcumin-treated colonic mucosa. We reported chemopreventive properties of curcumin (2,000 ppm) in inhibiting development of ACF and colon adenocarcinomas in AOM-induced F344 rats (Rao et al. 1995). Dietary administration of curcumin resulted in >50 % inhibition of AOM-induced colon adenocarcinoma incidence and multiplicity. Kawamori et al. (1999) reported a 78 % suppression of progression from adenoma to adenocarcinoma in a preclinical animal model with a high dose (6,000 ppm) of curcumin. Curcumin has been tested in combination with green tea catechins, another class of natural agents, and also in combination with the synthetic COX-2 inhibitor celecoxib for increased efficacy with low doses or to increase its bioavailability for better efficacy (Xu et al. 2010; Shpitz et al. 2006).

Although curcumin is well known for its anti-inflammatory and anti-tumorigenic properties in preclinical animal models, the absorption required for achieving its anti-tumor properties is still a concern. Clinical trials to assess pharmacokinetics, metabolism, and systemic bioavailability in cancer patients are inconclusive. Cheng et al. (2001) conducted a phase 1 clinical trial on cancer patients and reported poor absorption and minimal serum concentrations of curcumin. Another phase 1 study reported similar poor absorption of curcumin in patients (Sharma et al. 2004). However, Garcea et al. (2005) reported pharmacologically efficacious levels of curcumin (12.7 ± 5.7 nmol/g) in both malignant colorectal tissue and normal colorectal tissue (7.7 ± 1.8 nmol/g) from CRC patients, suggesting a potential anti-tumorigenic role for curcumin in CRC. Three other clinical trials have investigated the use of curcumin (curcumin, demethoxycurcumin, or bisdemethoxycurcumin) therapy in patients with established CRC and reported a decrease in carcinogenic embryonic antigen and PGE₂ levels (Sharma et al. 2001, 2004). Another trial of curcumin in CRC patients required high doses (3.6 g daily) to observe any effects on oxidative DNA adducts, and COX-2 markers (Garcea et al. 2005). In that study, no change in COX-2 protein was observed. Additional studies are in progress to develop curcumin formulations, analogs, and tumor site delivery methods to increase bioavailability for prevention and treatment of CRC.

Piperine, the principle bioactive compound of *Piper nigrum* and *Piper longum*, is included in many traditional formulae to enhance the effectiveness of other bioactive compounds, such as curcumin. Piperine has been reported to have immunomodulatory, anti-carcinogenic, anti-asthmatic, stimulatory, hepatoprotective, and anti-inflammatory (Darshan and Doreswamy 2004). It was found to be genotoxic but had no adverse effects when tested for toxicity profile in rats at doses 5–20 times the normal human intake (Bhat and Chandrasekhara 1986; Piyachaturawat et al. 1983). Due to its apolar nature, piperine alters lipid dynamics and it changes the conformation of enzymes in the intestine. Due to its unique properties, it is used in combinations to enhance the bioavailability of the other drugs. Its potential to increase the bioavailability of drugs in humans is of great clinical significance (Bajad et al. 2003). Nalini et al. (2006) reported inhibitory effects of piperine

on DMH-induced colon tumors in F344 rats. We reported inhibitory effects of piperine on AOM-induced colon tumors in F344 rats. The potential of piperine to enhance the bioavailability of other potent drugs is an important property that can be exploited to increase the efficacy of agents that inhibit CRC.

Another bioactive molecule available in edible fruits is resveratrol. The chemopreventive function of resveratrol was reported by Jang et al. (1997). They showed that it inhibited cellular events associated with the initiation, promotion, and progression of cancer development. A clinical trial with whole grape extract in patients with colon cancer resulted in reduced the expression of Wnt target genes in normal mucosa with no change in colon tissue (Nguyen et al. 2009). These trial results need more careful evaluation because of lack of control for dietary intake of resveratrol-rich food and the absence of control for ingestion of confounding medications. A second trial in 20 selected histologically confirmed CRC patients administered trans-resveratrol during 8 days prior to surgical resection reported a 5 % ($p = 0.05$) reduction in cell proliferation (Patel et al. 2010). The cell proliferation analysis was carried out preintervention and postintervention with resveratrol in tissue samples. These data suggest achievement of high enough concentrations of resveratrol in the intestinal tissues to show some inhibition of cell proliferation. However, some preclinical and clinical studies suggest that bioavailability of resveratrol is low due to poor absorptions as a result of intestinal metabolism and low activity of ATP-binding cassette (ABC) transporters (Juan et al. 2010, 2012; Alfaras et al. 2010a; Walle 2011; Cottart et al. 2010). In a preclinical animal model in which ACF are induced by DMH, an oral dose of 60 mg/kg resveratrol caused 50 % inhibition in the medial and 48 % inhibition in the distal tumors in rats (Alfaras et al. 2010b). Resveratrol also was observed to have inhibitory effects on mucin-depleted foci (MDFs) with reduction of the number of MDFs by 36 and 53 % in the medial and distal colon, respectively (Alfaras et al. 2010b). It also was found to be effective in long-term preclinical assays with development of adenocarcinomas as an end point. Oral administration of resveratrol (0.2 mg/kg in drinking water) for 100 days showed reduced ACFs and colon carcinogenesis in F344 rats (Tessitore et al. 2000). This reduction probably was due to modulation of Bax and p21, which regulate cell proliferation and apoptosis (Fig. 2.1). Daily administration of 8 mg/kg of trans-resveratrol for 30 weeks in DMH-treated rats resulted in reduction in the incidence and multiplicity of ACFs and also decreased formation of multicrypt (more than 6) ACFs (Sengottuvelan and Nalini 2006). Inhibition of ACFs with 6 or more crypts is an indication of potent chemopreventive efficacy via suppressing the progression of preneoplastic lesions to neoplasia. These results suggest that resveratrol possesses chemopreventive properties and can suppress the progression of preneoplasia to malignant neoplasia in colon. This study also reported inhibitory effects of resveratrol on polyamine synthesis, which is high in neoplastic tissues (Sengottuvelan and Nalini 2006).

Resveratrol also has been evaluated for its anti-tumor activity in genetically modified mice. Resveratrol (0.01 % in drinking water) decreased the number of tumors in the small intestine and completely suppressed tumor formation in the colon of APC^{Min/+} mice (Schneider et al. 2001). In contrast to these results,

Ziegler et al. (2004) reported null results with resveratrol in APC^{Min/+} mice. Even though this study used high doses of resveratrol (4, 20, and 90 mg/kg body weight) in pellet form, no difference was observed in incidence of intestinal tumors. Another Apc min mouse study reported a 27 % decrease in adenoma formation by 60 mg/kg of resveratrol administered in the diet (Sale et al. 2005). This reduction was attributed to decreases (of 58 and 62 % compared with intestinal mucosa from mice on control diet) in PGE₂, which is involved in the maintenance of the malignant phenotype (Sale et al. 2005). Evidence from all of these studies suggests that resveratrol has potential prevention and therapeutic properties and needs further evaluation for its dosage and clinical efficacy in CRC.

Diosgenin, a natural steroidal saponin found predominantly in fenugreek and wild yams, has diverse biological properties (Raju and Mehta 2009). The commercial synthesis of steroid products, such as cortisone, pregnenolone, and progesterone, involves use of diosgenin as a precursor (Raju and Mehta 2009). It is considered safe since it is neither synthesized nor metabolically converted into steroid by-products in the mammalian body. In preliminary studies with human subjects, diosgenin has been found to be effective against hyperglycemia (McAnuff et al. 2005), hypercholesterolemia (Juarez-Oropeza et al. 1987; Son et al. 2007), and hypertriacylglycerolemia (Kwon et al. 2003). Significant anti-inflammatory functions have been demonstrated in relevant animal models. It is used in rats to heal the GI toxicity generated by indomethacin treatment. Its anti-inflammatory role has been explored further by Yamada et al. (1997). Preclinical animal studies with AOM-induced ACFs in F344 rats suggested that diosgenin possesses chemopreventive efficacy in CRC. Administration of 0.1 or 0.05 % diosgenin in the diet during initiation, postinitiation, or promotion stages of colon carcinogenesis dose-dependently decreased ACF formation (Raju et al. 2004). Another study investigated the preventive effects of diosgenin (20, 100, or 500 mg/kg) on AOM/dextran sodium sulfate (DSS)-induced CRC in mice. Diosgenin at very low doses significantly inhibited (53, 46, and 40 %, respectively) colonic mucosal ulcers and dysplastic crypts induced by AOM/DSS treatment and also reduced expression of inflammatory cytokine genes, including IL-1 β , IL-6, IL-12b, and TNF- α , which are significantly elevated in the colonic mucosa of mice treated with AOM/DSS (Fig. 2.1). These studies suggest that diosgenin is a potent bioactive molecule possessing both anti-inflammatory and anti-tumorigenic properties that make it ideal for further investigation of its molecular and anti-neoplastic functions in human clinical trials.

Triterpenoids are isolated from various medicinal plants and have been studied for their anti-inflammatory properties. Mostly these compounds are non-toxic and have made their way into cosmetics and health products (Liu 1995). Recently, interest in understanding and elucidating the biological roles of triterpenoids for their hepatoprotective, analgesic, anti-tumor, anti-inflammatory, and immunomodulatory effects is increasing (Mahato and Sen 1997; Liu 1995). These agents are broken down in the gut to release triterpene metabolites, which are integrated into the intestinal cell membranes, absorbed, and lead to modulation of signaling pathways. These molecules inhibit expression of inflammatory genes such as

COX-2, iNOS and various inflammatory cytokines that are known enhancers of carcinogenesis (Janakiram et al. 2008; Rao et al. 2002, Raju et al. 2004) (Fig. 2.1). Recently, triterpene analogs that are more potent than the original parent molecules have been synthesized. Kawamori et al. (1995) found that oleanolic acid (ONA), a crude plant extract of triterpenoid at a dose of 200 ppm, was effective in reducing ACF in the intestine of F344 rats. We reported the anti-neoplastic properties of ONA and the analog 18 α -olean-12-ene-3 β -23,28-triol (OT) in AOM-induced ACFs in F344 rats (Janakiram et al. 2008). These triterpenoids significantly suppressed carcinogen-induced colonic preneoplastic lesions at dietary doses of 750 and 1,500 ppm of ONA, and 250 and 500 ppm of OT and without any toxicity. ONA inhibited 52 % of total AOM-induced ACFs and ~66 % of ACF with four or more crypts. OT inhibited up to 48 % of total AOM-induced ACF formation and 60 % of ACF with four or more crypts at very low doses compared with those of ONA. These studies support chemopreventive effects of triterpenoids in CRC and suggest that an in-depth evaluation of these agents in clinical trials should be carried out to assess pharmacokinetics, bioavailability, and anti-neoplastic functions.

Epidemiological, experimental, and clinical studies provide evidence for anti-CRC activity of omega (ω)-3 PUFAs. Evidence from animals and humans suggest that ω -3 PUFAs may play an inhibitory role during different stages of CRC, from primary CRC prevention to “tertiary” prevention after treatment of CRC and advanced metastatic disease. Out of 8 reported clinical studies of ω -3 PUFAs supplementation, 6 reported protective effects. In patients with a previous history of sporadic colorectal adenomas, oral supplementation with ω -3 PUFA has resulted in a 13–70 % reduction in intestinal epithelial cell proliferation as compared to placebo groups (Cockbain et al. 2012). A phase III randomized, double-blind, placebo-controlled trial investigated treatment with eicosapentaenoic acid-free fatty acid (EPA-FFA) in 58 patients with FAP who had previously undergone colectomy and ileorectal anastomosis and showed a 22.4 % reduction in polyp number compared with placebo (West et al. 2010). Colon cancer xenograft studies showed consistent protective effects (40–60 % reduction in xenograft size) in mice supplemented with ω -3 PUFAs as compared to untreated mice (Boudreau et al. 2001; Kato et al. 2002; Calviello et al. 2004). Similar beneficial results were reported from studies with CRC cell allograft tumors (Mund et al. 2007; Cannizzo and Broitman 1989; Togni et al. 2003; Pizato et al. 2005). In spite of these encouraging data, no published studies yet have investigated the anti-neoplastic effect of ω -3 PUFAs in patients with primary or metastatic CRC.

Fish and fish oil are rich sources of the ω -3 PUFAs EPA and DHA. The metabolites derived from these PUFAs result in formation of 3-series prostaglandins, which are anti-inflammatory rather than pro-inflammatory and also may possess anti-tumor properties. A report of a switch from 2 series PGE₂ to 3 series PGE₃ was demonstrated in colonic mucosa of rats treated with fish oil (Vanamala et al. 2008). The recently discovered anti-inflammatory lipid mediators RVs and LX derived from EPA and DHA are gaining importance for their anti-neoplastic functions. RVs derived from EPA are called as “E” series. Protectins are also generated

from precursors of omega 3-PUFAs. RVs or protectins from DHA, named “D” series, possess anti-inflammatory and immunomodulatory properties. The concentration required for these lipid mediators to exhibit any biological activity is in the nanomolar or picomolar range. Acetylation of aspirin by COX-2 in the presence of EPA results in formation of 5,12,18*R*-trihydroxy-EPA (18*R*-*RvE1*) (Janakiram et al. 2011) (Fig. 2.1). Ingestion of aspirin and EPA generated 18*R*-*RvE1* that was detectable in plasma of healthy volunteers (Oh et al. 2011). The anti-inflammatory role of *RvE1* is well documented in a mouse model of DSS-induced colitis; it acts through inhibition of phosphorylation of NF- κ B (Ishida et al. 2010). Another study reported a protective role of *RvE1* in mouse colitis through induction of intestinal alkaline phosphatase (Campbell et al. 2010). EPA and DHA exhibited protective effects against colitis in a rat model by restoring the number of mature, mucin-filled goblet cells (Arita et al. 2005). Two other studies also reported protective effects of *RvE1* against colitis induced by DSS and 2, 4, 6-trinitrobenzene sulfonic acid (Nieto et al. 2002; Ishida et al. 2009).

Lipoxin A₄ (LXA₄) was shown to inhibit neutrophil chemotaxis, adherence, transmigration, and activation during resolution of inflammation and suppression of IL-8 production by epithelia and leukocytes and to cause clearing of neutrophils by up-regulation of monocyte ingestion (Serhan 1997, 2002; Canny et al. 2002). Decreased LXA₄ expression was shown in a DSS-induced colitis model (Gewirtz et al. 2002). Protective effects of LXA₄ analogs were observed in DSS and other chemically induced colitis animal models (Gewirtz et al. 2002; Fiorucci et al. 2001). The protective effects of these analogs are attributed for their LXA₄ receptor-mediated inhibitory effects on pro-inflammatory signaling pathways. 15-*epi*-LXA₄ is formed in the presence of aspirin; and some of the preventive or therapeutic effects of aspirin-like NSAIDs may be through these 15-*epi*-LX (Claria and Serhan 1995) (Fig. 2.1). The anti-inflammatory functions of these lipid mediators suggest a potential chemopreventive therapeutic strategy for inflammation-related diseases like CRC.

2.8 Conclusions

Epidemiological and clinical literature strongly implicates chronic inflammation in neoplastic diseases, especially in CRC. Different inflammatory molecules and signals play different roles during different stages of CRC development. AA metabolism, via COX-2 and 5-LOX pathways, generates a variety of lipid mediators that affect initiation, growth, and development of CRC. Current evidence from preclinical, clinical, and epidemiological studies supports a positive role for anti-inflammatory agents, particularly NSAIDs as inhibitors of CRC; however, these drugs can have GI and cardiovascular toxicities. Additional studies are needed to design analogs or derivatives of these agents, to manipulate doses and to select appropriate patient populations to provide increased safety without losing efficacy for CRC suppression. It also is important to develop other agents that can balance COX

and LOX inhibition, including natural agents like curcumin or synthetic agents like licoferone, to achieve safer toxicity profiles while retaining significant inhibition of CRC. Additional natural bioactive anti-inflammatory compounds are being identified to provide beneficial effects against colitis-induced inflammation and CRC. Many of these agents are well tolerated and may provide safe alternatives to existing, more toxic compounds. Increased consumption of EPA- and DHA-rich foods may reduce inflammation and its related CRC conditions. And other novel lipid mediators, such as LX, RVs and their analogs, need to be evaluated in CRC models for their effects on colon mucosal immunity against development of CRC.

Acknowledgements We want to acknowledge the Grant support NCI-R01-94962; NCI-CN-53300 for the work quoted in this chapter and Dr. Julie Sando for her scientific and language editing of this chapter.

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Inflammation and Cancer

Aggarwal, B.B.; Sung, B.; Gupta, S.C. (Eds.)

2014, XII, 490 p. 24 illus., 19 illus. in color., Hardcover

ISBN: 978-3-0348-0836-1