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**Eicosanoid pathway in colorectal cancer: Recent updates**

Tuncer S *et al.* Eicosanoids and colorectal cancer

Sinem Tuncer, Sreeparna Banerjee

**Sinem Tuncer, Sreeparna Banerjee,** Department of Biological Sciences, Middle East Technical University, Ankara 06800, Turkey

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**Correspondence to**: **Sreeparna Banerjee, PhD,** Department of Biological Sciences, Middle East Technical University, Ankara 06800, Turkey. banerjee@metu.edu.tr

**Telephone:** +90-31-22106468

**Fax:** +90-31-22107976

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**Abstract**

The enzymatic metabolism of the 20C polyunsaturated fatty acid (PUFA) arachidonic acid (AA) primarily through the cyclooxygenase (COX) and lipoxygenase (LOX) pathways lead to the production of bioactive lipids that have myriads of functions ranging from homeostatic responses in the cardiovascular system, induction and resolution of inflammation and modulation of immune responses to diseases associated with chronic inflammation, including the development and progression of cancer. Since chronic inflammation is an essential component in the development of colorectal cancer (CRC), it therefore not surprising that many of these eicosanoids are implicated in CRC. Oftentimes these autacoids work in an antagonistic and highly temporal manner in inflammation; therefore inhibition of the well-known pro-inflammatory COX-2 or 5-LOX enzymes may inhibit the formation essential derivatives, or shunting of substrates from one pathway to another, leading to undesirable side-effects. A better understanding of the different enzymes and the products formed is therefore essential not only for understanding the importance of these bioactive lipids, but also to design more effective drugs that solely target the inflammatory molecules in both chronic inflammation and cancer. In this review we have evaluated the cancer promoting and anti-cancer roles of different eicosanoids in colorectal cancer, highlighting the latest literature on the effects of these molecules not only in the tumor tissues, but also in the tumor microenvironment. We have thereby attempted to delineate the roles that these opposing bioactive lipids play in neoplastic transformation in CRC through effects on proliferation, apoptosis, motility and metastasis and angiogenesis.

**Key words**: Eicosanoids; Cyclooxygenase; Lipoxygenase; Colorectal cancer

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**Core tip:** Eicosanoids are bioactive lipids that are generated from polyunsaturated fatty acids (usually arachidonic acid) through highly regulated enzymatic pathways in many different cell types. These molecules are effective in small amounts and may act in an autocrine or paracrine manner, regulating some of the most important steps both in the development of acute inflammation and its resolution. Aberrant expression of the enzymes that help in the synthesis of these autacoids is frequently seen in diseases associated with chronic inflammation, including cancer.

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**INFLAMMATION AND COLORECTAL CANCER**

Tumors show the characteristics of inflamed tissue, including immune cell recruitment into the tumor and surrounding stroma[1]. Although the presence of leukocytes within tumors was initially thought to represent anti-tumor immune responses, a role for inflammation in tumorigenesis is now generally accepted. Epidemiologic and clinical studies indicate that in response to chronic inflammatory conditions, epithelial cells (transformed and/or normal) and tissue-resident immune cells locally secrete cytokines, chemokines, growth factors and pro-inflammatory mediators that recruit inflammatory cells from the circulation into the tumor site[2]. Furthermore, phenotypically, the immune cells that invade the local tumor microenvironment are different from the normal immune cells by maintaining the inflammatory milieu and promoting invasion and migration of the transformed epithelial cells[3].

Colorectal carcinoma (CRC) is among the best examples of inflammation-associated cancers[4]. During colorectal carcinogenesis, epithelial cells in the colon accumulate mutations leading to either inactivation or activation of certain target genes that provide a selective growth advantage, which result in the transformation of the normal epithelium to adenomatous polyp and finally to invasive CRC. The transformed epithelial cells then acquire the ability to secrete inflammatory mediators that act on pro-inflammatory leukocytes, endothelial cells and fibroblasts to establish a tumor-promoting reactive microenvironment. For example, epidemiological studies have shown a higher incidence of CRC in patients with a previous history of IBD (Inflammatory Bowel Disease) compared to the general population[5]. It has also become evident that inflammation is a significant factor in the progression of tumors; the regular use of non-steroidal anti-inflammatory drugs (NSAIDs) lowers the mortality from sporadic colon cancer and suppresses adenoma growth in familial adenomatous polyposis (FAP) patients who inherit a mutation in the tumor suppressor APC gene[6]. The pathology of CRC, in line with other solid malignancies, indicates the presence of innate immune cells, including neutrophils, mast cells, natural killer cells and dendritic cells that are recruited to the tumor to suppress tumor growth and angiogenesis[7]. This phenomenon is called immune-surveillance and helps in the early detection and elimination of transformed cells and preneoplastic aberrant crypt foci (ACF), which may progress into adenomas and adenocarcinomas in CRC. On the contrary, colorectal and colitis-associated tumorigenesis are associated with the presence of an inflammatory microenvironment that favors the inhibition of immune-surveillance and promotes the formation of tolerogenic environment with the release of growth factors, thereby supporting further tumor growth[8,9]. In addition to paracrine signaling by growth factors, cytokines, chemokines and oxygen radicals[10], bioactive lipids, derived from polyunsaturated fatty acids, are among the earliest signals released in response to injury or an inflammatory stimulus. The role played these small mediators in inflammation and its resolution has garnered a lot of interest lately[11,12].

**POLYUNSATURATED FATTY ACIDS**

Polyunsaturated fatty acids (PUFAs) that can be metabolized to bioactive lipids include arachidonic acid (AA), linoleic acid (LA), linolenic acid (LNA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). AA is a 20C polyunsaturated fatty acid (20:4n-6) that is usually esterified to the second carbon in membrane phospholipids and gives rise to a wide variety of lipid products called eicosanoids. AA is also known as an n-6 fatty acid, signifying the position of the carbon with the first double bond, considering the terminal methylene carbon group as the first carbon. AA is produced from linoleic acid (LA, 18:2n-6), an 18C essential fatty acid, through the subsequent action of desaturases and elongases primarily in the liver. The release of AA from the phospholipids in the outer nuclear membrane is achieved through the activity of phospholipases such as the calcium-dependent cytosolic phospholipase A2 (cPLA2). The free fatty acid can then be metabolized through enzymatic pathways such as cyclooxygenase (COX) and lipoxygenase (LOX) to generate 2-series prostaglandins (PGs) and thromboxanes (Txs) (COX pathway) or the 4-series leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs) (LOX pathway)[11,13] (Figure 1). The eicosanoids are highly potent, short-lived molecules that act locally, and have been strongly implicated in various different cancers, including CRC.

Long-chain PUFAs such as EPA and DHA, commonly known as n-3 fatty acids, are extensively found in fatty fish, but are not efficiently synthesized in humans[14]. Since these fatty acids are primarily obtained through the diet, increased consumption of fish oils can change the fatty acid profile of the plasma and the cell membranes in a time and dose dependent manner[15], primarily at the expense of AA. This would imply a decrease in the production of inflammatory AA-derived eicosanoids. This is indeed the case, since healthy human volunteers consuming EPA and DHA supplements for varying lengths of time showed decreased levels of PGs and LTs[16]. EPA, being a 20C highly unsaturated fatty acid and therefore classified as an eicosanoid, can also be metabolized by the COX and LOX pathways into 3-series PGs and 5-series LTs. However, these lipids cannot be efficiently recognized by the PG and LT receptors and are therefore considerably less potent in inducing inflammation[17]. Both EPA and DHA are also substrates for the production of the newly identified autacoids that are essential for the resolution of inflammation[18].

**EICOSANOID PATHWAYS AND COLORECTAL CANCER**

Bioactive lipids may modulate the incidence of cancer through several different mechanisms that include, but are not limited to, induction of inflammation, cellular oxidative stress, activation of receptors and cellular signaling pathways and alteration of membrane dynamics[19].

***COX-2-derived lipid mediators***

AA is metabolized to prostaglandins either by the constitutively expressed COX-1, or by COX-2, which is expressed when induced by inflammatory stimuli[20]. COX-2 is an immediate-early response gene that is not expressed in most cells but is highly induced at sites of inflammation and in the tumor microenvironment[21]. The primary prostaglandin PGH2 that is produced from AA can be further metabolized to a number of other prostaglandins of which PGE2 has been strongly implicated in the development of gastrointestinal tumors[22]. This prostanoid acts *via* four G-protein coupled receptors (EP1-4) and can enhance tumorigenesis through various mechanisms, including enhanced cell proliferation, suppression of apoptosis and induction of angiogenesis[23].

Elevated levels of COX-2 and the accompanying elevation of PGE2 are often seen in CRC, and COX-2 expression is correlated with a lower survival rate among CRC patients[24]. It is well accepted that there are concerted interactions between carcinoma cells and other cells in the tumor microenvironment, which contribute to cancer progression. PGE2 modulates cancer-associated immune suppression through the recruitment of T cells, CD8+ cytotoxic T cells, regulatory T cells, dendritic cells and myeloid-derived suppressor cells (MDSCs)[20]. Additionally, the secretion of PGE2 may enhance oxidative stress, leading to a state of low grade continuous inflammation characterized by the infiltration of neutrophils and macrophages, eventually leading to mitogenic signals[18]. PGE2 has been shown to stimulate macrophages to produce pro-inflammatory chemokines and cytokines, such as macrophage chemoattractant protein-1 (MCP-1), which are responsible for the recruitment of leukocytes from the circulation to local sites of inflammation[25]. MCP-1 levels were shown to be higher in intestinal epithelial cells and it was demonstrated that MCP-1 could stimulate COX‐2 expression as well as PGE2 and vascular endothelial growth factor (VEGF) release in human macrophages[26].

In the adaptive response, PGE2 mediated signaling may affect cytokine production by the antigen-presenting cells that may influence the functional phenotype of T cells (from the anti-tumor T helper 1 (Th1) responses to immunosuppressive Th2 responses) during priming[27,28]. In trinitrobenzene sulfonic acid (TNBS) induced colitis, a model of IBD, PGE2 was shown to worsen inflammation and disease severity by increasing neutrophil and Th17 cell infiltration to the colonic tissue[29]. Furthermore, by acting on its receptor EP4 on T cells and dendritic cells, PGE2 was shown to amplify IL-23–mediated Th17 cell expansion[30].

The pro-tumorigenic effects of PGE2 may also be mediated by Treg cells, which contribute to immune evasion by tumor cells in a variety of cancers. Increased expression of COX-2 and elevated PGE2 production in adaptive FoxP3-positive Treg cells within the tumors as well as in the mesenteric lymph nodes have been shown to contribute to an immunosuppressive microenvironment in CRC, facilitating tumor growth by suppressing effector T cells and inducing resistance to antigen-specific cancer immunotherapy[31,32]. A role of COX-2 in tumor immunity was also exhibited in COX-2 expressing colon cancer cell lines, where the expressions of FasL and TRAIL were shown to cause a counter-attack against cytotoxic T cells[33].

The overexpression of COX-2 is also frequently associated with the concomitant expression of microsomal PGE synthase-1 (mPGES-1), the terminal synthase that leads to the preferential production of PGE2[20,34]. Accordingly, in *Apc*-mutant mice, genetic deletion of mPGES-1 was reported to suppress intestinal cancer growth by reducing the size and number of ACF in a carcinogen-induced colon cancer model[36]. Together, these findings suggest that mPGES-1 has crucial roles during colon cancer progression relevant to promotion of inflammation, and targeting mPGES-1 may be a feasible option for cancer chemoprevention[35].

Interestingly, prostaglandins are also essential for the health of the gastrointestinal mucosa by maintaining mucosal integrity, promoting wound healing and limiting inflammation[36]. The absence of cPLA2 in mice was recently shown to globally reduce the formation of AA-derived bioactive lipids, along with increased mucosal ulceration and pro-inflammatory cytokine expression[34]. Mice with targeted deletion of COX-2 in the endothelial cells and myeloid cells treated with dextran sulfate sodium (DSS) presented with greater weight loss and worse clinical scores compared to the WT littermates. However, mice with targeted deletion of COX-2 in the colonic epithelial cells did not show susceptibility to DSS[37]. Additionally, mPGES-1-/- mice have recently been reported to show more extensive inflammation in the GI tract compared to the WT mice[34]. This could have resulted from a shift in the metabolism of prostaglandins; a loss in PGE2 was associated with a gain in PGD2, which has tumor suppressive functions[34,38].

Influx and efflux carriers such as the prostaglandin transporter (PGT) and multidrug resistance-associated protein 4 (MRP4), as well as the inactivation of prostaglandins (specifically PGE2) by hydroxyprostaglandin dehydrogenase 15-(NAD) (15-PGDH) can also regulate the availability and efficacy of prostanoids[20]. In fact, 15-PGDH is frequently down-regulated in a number of cancers, suggesting a tumor-suppressive role[11]. Overexpression of 15-PGDH in colon cancer cells was shown to strongly inhibit the tumor growth in immune-deficient mice. It was also demonstrated that colonic 15-PGDH expression was directly controlled and strongly induced by the activation of TGF-β, which has tumor-suppressive functions in colon cancer[39,40]. Therefore, the combined induction of COX-2 and inactivation of 15-PGDH in colon cancer can markedly increase PGE2 levels, which may allow cancer cells to escape immune surveillance.

Randomized clinical trials and observational studies have indicated that long-term use (at least 5 years or longer) of acetyl salicylic acid (ASA, Aspirin®), which inhibits both COX-1 and COX-2, leads to a significant reduction in the risk of development of colorectal, esophageal, gastric, biliary and breast cancer as well as their distant metastases[41]. Furthermore, daily use of ASA has been reported to specifically prevent the development of colorectal polyps and reduce the risk of development of sporadic CRC or CRC from Lynch syndrome[42-44]. Moreover, the use of ASA after the diagnosis of CRC can also improve survival, especially in patients with COX-2-overexpressing tumors[24]. A recent prospective, observational study of ASA and COX-2 inhibitor use either during or after chemotherapy as an adjuvant in stage III colon cancer patients indicated reduced cancer recurrence and mortality[45]. Moreover, ASA use was also associated with a greater reduction in the risk of development of colorectal tumors when the normal colonic mucosa had a higher expression of 15-PGDH[45].

Other prostaglandins produced in the eicosanoid pathway such as PGD2, have also been shown to down-regulate granulocyte infiltration into colonic mucosa at the early stages of TNBS induced inflammation[38,46]. More recently, it has been shown that mast cell-derived PGD2 can function as an inhibitor of colitis and colitis-associated cancer (CAC) in mouse models[47]. Taken together, the findings suggest that different COX-2-derived prostaglandins can have opposing effects on inflammation and selective modulation of these mediators may prevent tumor growth in CRC.

***LOX-derived lipid mediators***

PUFAs are oxygenated through the enzymatic action of LOXs into LTs and hydroxyeicosatetraenoic acids (HETEs), which also exert significant effects on the development and progression of human cancers[48]. Several different isoforms of LOX exist, including 5-LOX, 15-LOX-1, 15-LOX-2 and 12-LOX[13], which are named according to the position of the carbon atom in AA that these enzymes can oxygenate. Except 5-LOX, which is located on chromosome 10, most of the other LOXs genes are located on the short arm of chromosome 17 within a few megabases of each other[13,16]. Although AA is the preferred substrate for oxygenation for most LOXs, some of the isoforms are capable of oxygenating fatty acids esterified to phospholipids or cholesterol[49,50].

In humans, 5-LOX is highly expressed in cells of myeloid origin, especially in leukocytes[51]. This enzyme catalyzes the conversion of AA to 5S-hydroperoxyeicosatetraenoic acid (5-HpETE) and the subsequent conversion of 5-HpETE to LTA4. LTA4 can then be converted by LTA4 hydrolase to LTB4 and by LTC4 synthases to cysteinyl leukotrienes[52] (Figure 1). 5-LOX activity is exquisitely sensitive to various different stimuli, including the second messenger Ca2+, which can bind to the N-terminus of 5-LOX that also contains a hydrophobic domain, which in turn helps 5-LOX bind to phospholipids in the membranes[53]. Usually located in the cytoplasm as a soluble protein, in the presence of Ca2+, the enzyme may get phosphorylated and translocate to the nuclear or endoplasmic reticulum (ER) membrane, where with the help of the 5-LOX activating protein (FLAP), it catalyzes the oxygenation of AA[53]. Many stimuli that raise the level of intracellular calcium ions, such as antigens, microbes, cytokines and toxins, can therefore result in the production of LTs[53,54].

LTs are classified into two general categories: LTB4 and cysteinyl LTs (LTC4, LTD4 and LTE4)[55]. Playing key roles in the pathogenesis of inflammatory disorders including IBD, LTs typically stimulate quick and short-lasting events (*e.g.,* contraction of smooth muscles, phagocyte infiltration, increased vascular permeability), which are important in the pro-inflammatory context. These responses are mediated by G-protein coupled receptors: BLT1/2 for LTB4 and CysLT1/2 and GPR17 for the Cys-LTs[52,576].

5-LOX is overexpressed in tissues with chronic inflammation and in transformed cells. In patients with polyps and colon cancer, 5-LOX was shown to be up-regulated[57] whereas in the APCΔ468 mouse model of polyposis, the loss of 5-LOX was protective[58]. In the same model, by enhancing both the proliferation of intestinal epithelial cells and the recruitment of MDSC to the spleen, mesenteric lymph nodes and the primary tumor, 5-LOX metabolic products produced by the hematopoietic cells were shown to promote tumorigenesis[59]. Dietary administration of the 5-LOX inhibitor Zileuton to the APCΔ468 mice resulted in an overall reduction in systemic inflammation as well as a reduction in the polyp number and inflammatory infiltration into the lesions[59].

Overproduction of LTB4 in human colon cancer tissue is implicated in the pathogenesis of IBD. Besides, a strong expression of the LTB4 receptor BLT1 has been detected in human colon tissues[60]. These results indicate the importance of an inflammatory autocrine loop during the promotion and progression of colon tumors: the inflammatory mediators can cause intestinal epithelial cells to up-regulate the expression of enzymes needed for the biosynthesis of eicosanoids, including the CysLTs, as well as the signal transducing proteins, the CysLT receptors, thus providing a self-sufficient signaling mechanism for both maintaining inflammation and for tumor progression[58]. Taken together, these studies show that pro-inflammatory LTs could facilitate tumor growth through establishing an inflammatory microenvironment.

Metabolism of AA by 12-Lipoxygenase (12-LOX) leads to the production of 12-HETE, which has been shown to have growth stimulatory properties in a number of different cancer types[61]. Additionally, a Gln261Arg polymorphism in 12-LOX gene has been shown to be associated with enhanced susceptibility to several malignancies, which also indicates a potential oncogenic role for 12-LOX[62,63]. Although a recent meta-analysis including 8379 subjects revealed that this specific polymorphism was not associated with increased risk of colon cancer[64], some other studies demonstrated that 12-LOX expression was associated with an oncogenic phenotype in CRC[62]. 12-LOX was also shown to be up-regulated in colon cancer specimens that were associated with inflammation[61]. Moreover, 12-LOX expressing colon cancer cell lines were shown to migrate more either through the decreased expression of E-cadherin and integrin-β112], or through enhanced production of reactive oxygen species (ROS) and the activation of the catalytic subunit of the NADPH oxidase complex Nox1[65].

15-Lipoxygenase-1 (15-LOX-1), which can oxygenate AA, LA as well as complex substrates such as biomembranes[66], unlike 5-LOX and 12-LOX, may have an anti-inflammatory, tumor suppressive role in CRC. This enzyme can oxygenate AA to 15-HETE, or LA to 13(S)-hydroxyoctadecadienoic acid [13(S)-HODE]. Profiling of LOX metabolic products in CRC has indicated that 13(S)-HODE was the only metabolite to significantly increase in the Caco-2 model of cellular differentiation[67,68]. Additionally, an assay of over 120 cancer cell lines from 20 different cancer types indicated an almost universal loss of expression of 15-LOX-1 in the dedifferentiated cell lines compared to well-differentiated cancer cells or non-transformed cells[68]. 13(S)-HODE levels were also shown to be reduced in colorectal polyp samples from patients suffering from FAP compared to paired normal tissues[67]. The loss in expression of 15-LOX-1 is primarily epigenetic, such as through the nucleosomal remodeling and histone deacetylase (NuRD) complex[69] and re-expression has been reported either through histone methylation/demethylation and acetylation[70,71] or activation of transcription factors such as STAT-6[72]. In a mouse model with gut targeted expression of human 15-LOX-1 exposed to azoxymethane, the number of tumors was lower in the animals with transgene expression and the 15-LOX-1 expression was lower in the tumors compared to the normal tissues[73].

An inverse link between 15-LOX-1 expression and secretion of pro-inflammatory cytokines has been indicated in recent years. Gut-targeted expression of 15-LOX-1 resulted in lower levels of TNFα and inducible nitric oxide synthase (iNOS) in the epithelial cells[73]. In human CRC, downregulation of 15-LOX-1 was associated with increased expression of IL-1β[75]. This has been further substantiated by a loss of NF-κB (a key inflammatory transcription factor) signaling both in colon cancer cell lines and mouse models when 15-LOX-1 is re-expressed in the gut[73,75,76]. There is also evidence indicating that 15-LOX-1 expression can inhibit CAC. Chemical inhibition of 15-LOX-1 by PD146176 was shown to cause significant deterioration of intestinal functions in a murine model of experimental colitis[77]. While LA can be oxygenated efficiently by 15-LOX-1 leading to the production of 13(S)-HODE, AA can also be metabolized by both 15-LOX-1 and 15-LOX-2 to 15(S)-HETE[78]. 15(S)-HETE levels were reported to be significantly lower in the serum of colorectal cancer patients compared to controls[78].

Thus, through the opposing effects of various metabolites formed downstream of the enzymatic action of the different LOXs, activation of acute inflammatory responses, neoplastic transformation, or activation of anti-inflammatory and anti-tumorigenic pathways may occur. De-regulation of any of these pathways may therefore be expected to lead to a loss of homeostasis.

**EICOSANOIDS AND THE HALLMARKS OF CANCER**

Various types of cancer cells and surrounding stromal cells produce a high amount of pro-inflammatory eicosanoids. These bioactive lipid metabolites can modulate tumor progression through several mechanisms: direct activation of receptors on tumor epithelial cells, contributing to cell proliferation, apoptosis, migration and invasion, induction of epithelial cells to secrete growth factors, as well as secretion of pro-inflammatory mediators and angiogenic factors. Thus, these molecules can facilitate tumor growth, in addition to supporting tumor-associated angiogenesis and evasion of the immune system[20].

***Proliferation and apoptosis***

It is already well documented that tumor growth relies on the dysregulated balance of cellular proliferation and cell death. It is not surprising that various eicosanoids, generated through the metabolism of AA that can activate/inhibit important signaling pathways in cells, can also regulate cellular proliferation and apoptosis in colon cancer cells.

**COX-2 pathway in cell proliferation and apoptosis:** COX-2 is overexpressed in roughly 50%-80% of all colorectal cancers[79]. At the cellular level, overexpression of COX-2 was shown to increase cell-to-matrix adhesion and inhibit apoptosis in human colorectal cancer cells[80-82]. Furthermore, in the APCΔ716 mouse model, the number and size of the polyps were shown to be reduced dramatically when the COX-2 gene was knocked out[83]. In accordance with this finding, ASA and sulindac have been shown to reduce the number and the size of adenomatous colonic polyps in patients with FAP[84] and the use of conventional NSAIDs inhibited chemically-induced colon cancer in rodent models by inhibiting COX-2 activity[85]. It has been suggested that COX-2 can be induced through the wild-type p53-mediated activation of the Ras/Raf/ERK cascade, which can then block p53 or genotoxic stress mediated apoptosis in the human colon cancer cell line HCT-116. This anti-apoptotic effect can be a mechanism to diminish cellular stress associated with p53 induction[86]. On the other hand, use of NSAIDs inhibited the expression of the anti-apoptotic protein Bcl-XL, resulting in an altered BAX to Bcl-XL ration and enhamced apoptosis[87]. An increase in anti-apoptotic Bcl-2 and reduction in pro-apoptotic Bim expression by the COX-2-derived eicosanoid PGE2 has also been reported[21,88].

A considerable amount of crosstalk has been reported between the COX-2 and EGFR pathways. PGE2 treatment, for instance***,*** was shown to significantly increase cellular proliferation and to reduce apoptosis in a rodent CAC model[89] in addition to inducing COX-2 expression in intestinal adenomas by activating the MAPK signaling pathway[90]. PGE2 was shown to induce ERK2 signaling in colon cancer cell lines through the rapid phosphorylation of EGFR[91]. Inhibition of both EGFR and COX-2 through a targeted liposome carrying the COX-2 inhibitor celecoxib and a monoclonal antibody against EGFR (Cetuximab) has been shown to additively inhibit the proliferation of colon cancer cell lines expressing both EGFR and COX-2[92].

Roberts *et al*[93] have reported that during glucose deprivation, PGE2 can promote tumor cell survival in the colon through the activation of the PI3K/AKT pathway, which in turn could up-regulate COX-2 and down-regulate 15-PGDH. Moreover, glucose deprivation was also demonstrated to activate the unfolded protein response (UPR) resulting in the elevation of C/EBP-homologous protein (CHOP) expression levels, which was positively correlated with 15-PGDH expression. These data suggest that stress conditions can regulate PGE2 as a common and crucial mediator of cell survival during adaptation to the tumor microenvironment.

In the colorectal adenocarcinoma cell line DLD-1, PGE2 was shown to bind to EP2, which stimulated tumor growth by activating the PI-3K/AKT signaling followed by the activation of the β-catenin signaling pathway[94]. PGE2 can also induce proliferation in colorectal tumor through the EP4 receptor by inducing ERK phosphorylation[95]. Additionally, Park *et al*[96] have proposed that COX-2 inhibition can have significant anti-tumorigenic effects through blocking stroma-derived PGs as well. Using a co-culture model to evaluate cancer cell-stromal cell relationship, these authors reported that use of an EP4 antagonist resulted in decreased proliferation of COX-2 non expressing LS174T colon adenocarcinoma cancer cell line.

In contrast to PGE2, 15d-PGJ2 was shown to induce apoptosis[97] and cell cycle arrest in CRC cells[98] by inhibiting the activity of the inflammatory transcription factor NF-κB activity, reducing the levels of anti-apoptotic genes[97], down-regulating c-myc expression while upregulating c-Jun and GADD153[99]. When 15d-PGJ2 and histone deacetylase (HDAC) inhibitors were used in combination, they showed a synergistic effect on caspase-dependent apoptosis, leading to ROS generation and ER stress, decreased expression of anti-apoptotic proteins Bcl-XL and XIAP and increased expression of CHOP and DR5 (Death receptor 5, TRAIL-R2) in colon cancer cell lines. Furthermore, the same effects of the co-treatment were also seen *in vivo*, with an inhibition in tumor growth in a nude mice xenograft model inoculated with DLD-1 cells[100]. Shin *et al*[101] suggested that the growth inhibition and induction of apoptosis by 15d-PGJ2 in human and murine CRC cell lines was caused by the ROS dependent down-regulation of AKT and p-AKT.

**LOX pathway in proliferation and apoptosis:** The 5-LOX protein was shown to be overexpressed in the early stages of colon cancer, where its expression was significantly correlated with patient age, size of polyps, intraepithelial neoplasia and villous and tubulovillous adenoma, all of which are considered to be typical markers of transformed adenomatous polyps[102]. Inhibition of 5-LOX with Zileuton was shown to significantly decrease both colon cancer cell line proliferation as well as xenografted tumor size[57]. LTB4 was shown to have pro-carcinogenic effects in CRC through the activation of the ERK pathway[103]. Induction and/or accumulation of COX-2, β-catenin, and Bcl-2, as well as PGE2 production in non-transformed epithelial cells lining in the colon have also been reported in the presence of LTB4[104]. Furthermore, LTD4, a cysteinyl leukotriene, was reported to inhibit caspase 3, thereby increasing the resistance to NSAID-induced cell death[105].

In several different cancer types, COX-2 and 5-LOX signaling can converge to enhance cell proliferation[106]. For example, knock-out of 5-LOX or FLAP was shown to increase the COX-2 metabolites produced by inflammatory cells indicating that inhibition of one pathway can shunt the metabolism of AA towards the other pathway[107-109]. Dual inhibition of 5-LOX and COX-2 may lead to additive or synergistic effects on reducing cellular proliferation in colon cancer as shown by the combination of AA861 (5-LOX inhibitor) and celecoxib[110], the dual COX/5-LOX inhibitor licofelone[111], and the combination of celecoxib and MK886 (5-LOX inhibitor)[112]. Better understanding of these pathways will have important implications for cancer chemoprevention and treatment[18].

The role of 15-LOX-1 in proliferation and apoptosis of colon cancer was initially considered to be controversial, although well-controlled *in vitro* and *in vivo* studies in the past few years have revealed an unequivocal tumor suppressive role of the enzyme in CRC[113]. Initial studies indicated an anti-apoptotic role of the enzyme, primarily through the use of inhibitors such as NDGA (nordihydroguaiaretic acid), which may have pleiotropic effects in cells[114]. Yoshinaga *et al*[115] evaluated that 15-LOX-1 over-expression in colon cancer cell lines increased cell proliferation *via* the activation ERK followed by a decrease in p21(Cip/WAF1) expression. However, many other subsequent studies have shown that the main product of 15-LOX-1, 13(S)-HODE, can inhibit cell proliferation and induce apoptosis in CRC[116,117]. Moreover, the expression of 15-LOX-1 and levels of 13(S)-HODE were reduced in the polyps compared to paired normal tissues in patients with FAP[67]. Since mice express 12/15-LOX, an enzyme that can simultaneously metabolize AA to 12-HETE and LA to 13(S)-HODE, which have opposing effects on tumorigenesis, a transgenic mouse model was established that can express the human 15-LOX-1 specifically in the gut epithelial cells[74]. These mice showed decreased tumor incidence[73]. Interestingly, an inverse correlation between the expression of 15-LOX-1 and COX-2 has been proposed in the adenoma to carcinoma sequelae[118] leading to an accumulation of pro-tumorigenic PGs and a loss of the apoptotic 13(S)-HODE. It has been suggested that 15-LOX-1-mediated inhibition of NF-κB, which can transcriptionally up-regulate COX-2, leads to a loss of expression of the latter. Epigenetic silencing of 15-LOX-1 in the later stages of progression of CRC may lead to an increase in COX-2 expression, thus exacerbating the inflammatory milieu[119].

However, focusing on the effects of 15-LOX-1 expression only in the epithelial intestinal cells may not provide enough information about the contribution of its expression in CRC development. The effects of 15-LOX-1 and its metabolites in tumor associated stromal cells and endothelial cells are also required to understand the underlying mechanisms beyond the 15-LOX-1 signaling.

**NF-κB and PPAR signaling pathways driven by eicosanoids in CRC:** In colon cancer, the activity of NF-κB in the intestinal epithelial cells and myeloid cells in the tumor environment play an essential role in tumor formation[76]. Therefore, one may suggest that specific inactivation of the NF-κB pathway in cancer cells and surrounding myeloid cells may attenuate formation of inflammation-associated tumors[120].

Peroxisome Proliferator-Activated Receptors (PPARs) are ligand-activated transcription factors of nuclear hormone receptor superfamily that include PPARα, PPARγ and PPARβ/δ, each of which can mediate the physiological actions of a large variety of fatty acids and fatty acid-derived molecules that can act as ligands for these transcription factors (Figure 2). Activated PPARs can also function as transcriptional repressors of NF-κB, STAT-1 and AP-1 signaling[121]. PPARγ is known to be expressed in the normal colon, with reduced expression in colon tumors[122]; however, mutations of PPARγ in CRC are rare[123]. Agonists of PPARα and PPARγ were shown to inhibit DSS-induced colitis and formation of aberrant crypt foci in rats[124]. PPARβ/δ, on the other hand, is associated with pro-inflammatory pathways and the progression of CRC[121].

15d-PGJ2, a natural agonist of PPARγ, was shown to inhibit the proliferation of human colon cancer cells HT-29 through the upregulation of the tumor suppressive transcription factor Kruppel-like factor 4 (Klf-4)[125]. 15d-PGJ2 and rosiglitazone, a synthetic ligand of PPARγ, were found to suppress proliferation in the CRC cell line Caco-2 by repressing telomerase activity and telomerase reverse transcriptase (hTERT) expression through downregulation of c-Myc and the upregulation of Mad1[126].

13(S)-HODE, produced in the 15-LOX-1 pathway, can act as a ligand for PPARγ[127]. Re-expression of 15-LOX-1 in colon cancer cells was shown to down-regulate PPARδ, thereby promoting the induction of endogenous PPARγ target genes related to the induction of apoptosis[129]. Supporting this finding, over-expression of 15-LOX-1 was associated with decreased proliferation and increased apoptosis, also reduced cellular motility, anchorage-independent growth, migration, and cell invasion in colon cancer cells [118]. Moreover, increased 13(S)-HODE-mediated PPARγ activation was proposed to inhibit the activation of NF-κB, which was associated with decreased cell *via*bility[75]. In colitis and CAC[124], 15-LOX-1 activity was also shown to activate PPAR-γ[128,129], which suppressed the expression of key inflammatory genes most likely through the inhibition of NF-κB[130,131].

13-(S)HODE has been shown to suppress PPAR-δ; the latter can transcriptionally upregulate the expression of IL-6, thereby promoting colitis and CAC[128,132,133]. Very recently, 15-LOX-1-induced inhibition of PPARδ during the promotion of CAC was shown to be mediated through the suppression of IL-6 expression, STAT3 phosphorylation, and Notch3 expression[134]. PPARδ has been also implicated in the pathogenesis of CRC[69,135] with its elevated expression[136]. A positive correlation of PPARδ expression with late stages of CRC has also been observed[137]. PGI2 was shown to activate PPARδ, which may lead to a loss of apoptosis through the sequestering of pro-apoptotic protein BAD by 14-3-3 epsilon and reduced mitochondrial damage[138]. Similarly, stromal PGI2 generation was claimed to promote cell survival in colonocytes through PPARδ activation[139]. Furthermore, PPARδ activation was also associated with the increased expression of growth factors such as VEGF in colon carcinoma cells[*69*]. More recently, hypoxia was proposed to stimulate the transcriptional activation of PPARδ through p300 and the PI3K/AKT pathway, resulting in the expression of IL-8 and VEGF *in vivo*[140].

***Metastasis***

Although surgery is the most curative approach for CRC, approximately 40% of treated patients eventually show either local recurrence or distant metastases[141,142], primarily to the liver and lungs[143]. Both experimental and clinical studies have shown that daily use of ASA was associated with a reduced risk of metastasis[144] and inhibited the spread of primary tumor cells to other organs post diagnosis[145], giving a role for eicosanoids and eicosanoid-mediated signaling in CRC metastasis.

**COX pathway and metastasis:** Metastasis is a well-regulated cascade of events that requires the coordinated activation of a number of factors expressed/released not only by the tumor cells but also the stromal cells. PGE2 is claimed to promote a more metastatic phenotype in CRC[1467]. Analysis of sporadic colorectal adenocarcinoma tissue samples showed a significant relationship between COX-2-derived PGE2 levels and tumor stage: higher PGE2 levels were reported in metastatic tumor specimens than in tumor specimens without any metastases. Thus, it can be concluded that PGE2 amounts may be correlated with tumor aggressiveness, ability to metastasze and patient prognosis[147].

Epidemiological, clinical, and animal studies have demonstrated that COX-2 and epidermal growth factor (EGF) signaling pathways play key roles, coordinately in promoting CRC growth and metastasis[148]. For example, the expression of EGFR was directly correlated with the potential of human CRC cells to metastasize to the liver[150]. Moreover, Buchanan *et al*[150] suggested that in developing CRC, the early effects of PGE2 are mediated by EGFR transactivation and subsequent phosphorylation which is responsible for the down-stream effects, including cell migration and invasion. In their following reports, the same group showed that PGE2 induced an EP4/β-arrestin1/c-Src signaling complex, which resulted in EGFR transactivation and downstream Akt signaling to stimulate CRC cell migration i*n vitro* as well as metastatic spread to the liver *in vivo*[151]. In the presence of functional EGFR, PGE2 was also shown to transactivate hepatocyte growth factor receptor (c-Met-R), thereby increasing phosphorylation and accumulation of the oncogene β-catenin, and inducing urokinase-type plasminogen activator receptor (uPAR) expression resulting in increased CRC cell invasiveness[152]. A significant decrease in liver metastasis with the use of selective EP4 receptor antagonists has also been reported[153]. In another report, PGE2 treatment was showed to activate JNK1/2 kinase, followed by the increase in the protein levels of the migration-related factors uPA and MMP-9, which further promoted cellular motility in the human colon cancer cell line LoVo. However, 17β-Estradiol pre-treatment downregulated the expression of uPA and MMP-9 *via* deactivation of JNK1/2, and inhibited PGE2-induced LoVo cell motility. Based on these findings, the authors suggested that the incidence and mortality rates of CRC in women are lower than in men, because of a protective role of estrogen against the development of fatal colon cancer and a reduced mortality from this disease[154].

In contrast to PGE2, PGI2 is known for its anti-metastatic effects in CRC. PGI2 analogues were suggested to protect against metastasis by inhibiting CAM (Cell Adhesion Molecule) -mediated adherence of colon carcinoma to endothelial cells in metastatic target organs[155].

**LOX pathway and metastasis:** Data on the contribution of the LOX enzymes in colon cancer migration and invasion have been emerging recently[156]. In one study, the selective LOX inhibitor, NDGA, was found to decrease in the motility of human colon cancer cells, which was partly explained by the inhibition of MMP-2 and 9[157]. Loss of 15-LOX-1 expression was found in lymph node and liver metastases of pancreatic cancer[158], and 15-LOX-1 re-expression in CRC cell lines inhibited their invasiveness, motility, and migration[117]. More recently, Wu *et al*[159] showed that 15-LOX-1 re-expression in HCT116, HT29 and LoVo colon cancer cells inhibited cell survival, angiogenesis, cancer cell migration and invasion.

***Angiogenesis***

For tumors to grow and metastasize, it is essential to generate their own blood supply, a process defined as neo-angiogenesis. Many cells in the tumor microenvironment, including tumor epithelial cells, stromal cells and immune cells, secrete various pro-angiogenic factors for proliferation, migration, capillary tube formation, and recruitment of endothelial cells[160]. A large number of *in vitro* and *in vivo* studies have shown that eicosanoids can modulate angiogenesis at different levels[20].

VEGF is a major regulator of angiogenesis, and its expression is up-regulated in response to multiple micro-environmental “stress” factors, such as hypoxia, acidosis and starvation; which are all related to poor blood supply. In tumors, hypoxia can lead to the stabilization of the transcription factor HIF-1α, which activates genes with the hypoxia-responsive element (HRE) in their promoters, like VEGF. VEGF exerts its effects on target cells through tyrosine kinase receptors including VEGF receptor 1 (VEGFR1, Flt1) and 2 (VEGFR-2, Flk-1/KDR)[161]. The ligand binding induces receptor dimerization and the activation of downstream signaling pathways including the MAPK family, PI3K/AKT or protein kinase C (PKC)[161]. Besides hypoxia, other factors that have been shown to stimulate VEGF expression include ROS[162], growth factors[163], cytokines[164], and lipid mediators such as PGE2[165-168].

**COX pathway in angiogenesis:** PGE2 stimulation has been shown to induce HIF-1α stabilization[163] and VEGF expression i*n vitro*[169]. In addition, VEGF and COX-2 expressions and tumor angiogenesis were shown to be highly correlated in colon cancer samples[147,170]. Through its receptor EP2, PGE2 was shown to stimulate the nuclear translocation of β-catenin[94], whereby it activated T cell factor 4 (TCF-4) and HIF-1α that triggered cell survival, proliferation and angiogenesis in colon cancer[171,172]. Homozygous knock-out of EP2 completely abrogated the induction of VEGF in the intestinal polyp stroma of APCΔ716 mice and decreased the number and size of intestinal polyps, showing that PGE2-directed induction of VEGF is an important factor for tumor growth[173]. Moreover, PGE2 was shown to induce the expression and release of the pro-angiogenic chemokine CXCL1 in CRC, which in turn stimulated microvascular endothelial cell migration and tube formation in both *in vitro* and *in vivo*[174]. PGE2 stimulation of the EP3 receptor was shown to enhance cellular migration *via* the up-regulation of VEGFR-1 expression in the human colon cancer cell line HCA-7, which endogenously expresses EP3 receptors[154]. Hypoxia was shown to induce EP1 expression in colon cancer cells, while EP1 inactivation inhibited PGE2 dependent and hypoxia inducible expression of angiopoietin-like protein 4 (ANGPTL4), the lipid metabolizing functions of which have been well established through the inhibition of lipoprotein lipase (LPL)[175].

In addition to inducing a range of angiogenic factors in epithelial cells, PG signaling in the surrounding stromal cells also supports angiogenesis in colon cancer. For example, PGE2 and TXA2 were reported to regulate the adhesion and spreading of human umbilical vein endothelial cells (HUVEC), through the cAMP-dependent activation of protein kinase A (PKA) and cAMP- and PKA-dependent activation of Rac, respectively[176]. Besides VEGF, PGE2 also may mediate the angiogenic effects of basic fibroblast growth factor (bFGF) by up-regulating the expression of the C-X-C chemokine receptor type 4 (CXCR4) in human microvascular endothelial cells (HMECs) and enhancing cellular response to stromal-derived factor 1 (SDF-1), a unique ligand for CXCR4[177]. TXA2 was also shown to enhance endothelial cell migration and angiogenesis[178]. An increase in TXA2 levels, as a result of overexpression of TXA2 synthase in C-26 colon adenocarcinoma cells allografted to BALB/c mice, was reported to show accelerated tumor growth and tumor-associated angiogenesis[179].

The process of angiogenesis may require not only a crosstalk between tumor epithelial and endothelial cells, but also the involvement of immune cells which produce pro-angiogenic factors. PGE2 has been shown to induce mast cells to release VEGF and the chemokine CCL2[180,181], which can induce tumor-associated angiogenesis[191] by directly recruiting CCR2 expressing endothelial cells[192] and inducing VEGF release from macrophages[26]. Contrary to the pro-angiogenic role of the COX pathway described above, PGE2, through its receptor EP2 was shown to inhibit the secretion of VEGF in Caco-2 colon cancer cells exposed to hyperosmotic stress[182]. Additionally, 15d-PGJ2 was shown to down-regulate the expression of COX-2 and VEGF in colon carcinoma cells by inhibiting the transcription factor AP-1[183]. In an *in vivo* study in which PGI2 synthase was retrovirally transduced to C-26 colon adenocarcinoma cells and subsequently grafted to syngeneic BALB/c mice, the increased production of PGI2 resulted in slower tumor growth and less vasculature[179].

When all these findings are considered together, it may be possible to suggest that the relative levels of pro- and anti-angiogenic prostanoids in the tumor microenvironment might be strong determinants in the angiogenic outcome of colorectal tumors.

**LOX pathway in angiogenesis:** A growing body of evidence indicates that the LOX-catalyzed products, LTs and HETEs also exhibit important biological effects on angiogenesis in colon cancer. Ye *et al*[184] implicated 5-LOX in the promotion of colon cancer growth by nicotine through the up-regulation of VEGF, MMP-2 and MMP-9, thus stimulating the angiogenic process in the colon. The same group also reported that cigarette smoke extract indirectly stimulated endothelial cell proliferation, a biological phenomenon that can enhance neoangiogenesis[185,186]. CysLT1R antagonists were shown to impair angiogenesis in colon cancer xenografts[187], while LTB4 was reported to induce neutrophil-mediated vascular permeability[188]. In addition, LTB4 enhanced hypoxia-induced microvascular alterations *in vivo*[189]. The LTB4 receptor BLT2 expression was found to be highly inducible by VEGF, which suggested a potential interplay among VEGF, BLT2, and BLT2 ligands in vascular angiogenesis[190]. Similarly, LTC4 and LTD4 also promoted angiogenesis *via* a receptor-mediated interactions[191]. Moreover, a reduction in vascular permeability was observed in LTC4 synthase knock-out mice where the synthesis of cysteinyl LTs was impaired[192].

There has been very few reports on the role of 15-LOX-1 in neo-angiogenesis in colorectal cancer. Recently, we and others have shown that the re-expression of 15-LOX-1 in colon cancer cell lines could reduce the expression and secretion of VEGF-A, and treatment of HUVECs with conditioned medium from colon cancer cell lines ectopically expressing 15-LOX-1 showed reduced tube formation[159,193]. However, the signaling mechanism through which such an angiostatic effect was observed has not yet been reported.

Therefore, as with the prostanoids, it is likely that the different bioactive lipids produced from the LOX pathway may have contrasting effects on angiogenesis and the ultimate functional effect may be decided by the balance between the pro- and anti-angiogenic products.

**EICOSANOIDS IN THE RESOLUTION OF INFLAMMATION**

The resolution of acute inflammation, rather than being a passive process of diluting out pro-inflammatory mediators, was shown to be actively conducted by a number of bioactive lipid mediators[194].The timely resolution of inflammation prevents the development of chronic inflammation and fibrosis, and enables the organism to return to homeostasis[194].

The primary drivers of resolution include cessation of neutrophil infiltration and the nonphlogistic recruitment of macrophages to clear the debris at the site of inflammation[194]. As a mediator of these processes, lipoxins (Lx) were the first bioactive lipids identified. Lx’s can be synthesized from AA through the enzymatic action of 5-LOX in neutrophils; the LTA4 synthesized can be converted to LXA4 and LXB4 by 12-LOX in platelets when the latter adhere to neutrophils[195] (Figure 1). Additionally, AA may be metabolized by 15-LOX-1 and the oxygenated product can be converted to an epoxytetraene and then to LXA4 or LXB4 with the action of hydrolases. ASA leads to the acetylation of COX-2, shifting the activity of the enzyme from the production of pro-inflammatory prostanoids to the production 15(R)-HETE, which is subsequently metabolized by 5-LOX to 15-epi-Lx or aspirin triggered lipoxins (ATLs)[18]. Many of these bioactive lipids act through G-protein coupled receptors such as the lipoxins receptor/formyl peoptide receptor (ALX/FPR2), which bind to LXA4 and ATLs[18].Although most of the autacoids involved in resolution are known to be synthesized in a transcellular manner, involving at least two cell types, a recent study indicates that lipoxins may also be generated from a single immune cell[196].

LXA4 expression or administration of LXA4 analogs was shown to reduce DSS-induced colitis[197]. Inflammatory stimuli in the intestinal epithelial cells have been shown to result in a feedback loop to up-regulate the expression of LXA4 receptor in intestinal epithelial cells[198]. Additionally, co-culture of Caco-2 cells with macrophage cells where the cells were also treated with LXA4 exhibited a decrease in secretion of pro-inflammatory cytokines[199], most likely due to the inhibition of NF-κB. In a recent study involving colonic biopsies from patients under remission from ulcerative colitis, a significant increase in the levels LXA4 along with enhanced expression of FPR2/ALX receptor mRNA as well as increased level of macrophage infiltration was observed indicating that LXA4 levels may play an important role in the restoration of mucosal homeostasis[200]. The expression of FPR2 was also shown to be increased in the colon of patients with Crohn's disease again indicating that signaling through lipoxin is enhanced in inflammatory environments most likely to enhance the clearance of debris or bacteria by macrophages[201].

Resolvins (Rvs) are derived from the n-3 fatty acids EPA (E-series Rvs) and DHA (D-series Rvs) through the concerted actions of acetylated COX-2, 5-LOX or 15-LOX[18] (Figure 1). Rvs have shown potency at very low concentrations when administered orally or intravenously[18]. Rvs are known to signal through *ChemR23* and chemokine-like receptor 1 (CMKLR)[18]. Resolvins (RvD1 and RvD2) have been shown to be chemopreventive in CAC in mice, along with reducing tumor growth[202]. RVE1 was reported to induce neutrophil clearance into the lumen of the gastrointestinal tract[203]. Moreover, RVE1 was shown to inhibit the phosphorylation and activation of p65 NF-κB in the distal colons of a DSS-colitis mouse model[199], indicating roles in both pro-resolution and anti-inflammatory pathways. Interestingly, the enzyme intestinal alkaline phosphatase (ALP1) was shown to be induced in epithelial cells in the presence of RvE1, along with a role in protection from colitis[204]. Many of these potent bioactive molecules are currently undergoing large-scale clinical trials[205].

Mareisins (MaR) are generated in macrophages from DHA through the action of macrophage 12-LOX[202]. Intermediates formed during the conversion of DHA to MaR1 were shown to inhibit the formation of LTB4, inhibit the oxygenation of AA by 12-LOX and enhance the conversion of the M1 inflammatory macrophages to the M2 phenotype[202]. Yet another intermediate that has been identified recently includes 13,14-dihydroxydocosahexaenoic acid (13,14-diHDHA or MaR2) that is synthesized when macrophages are co-incubated with 12-LOX and soluble epoxide hydrolase (she). This compound reduced neutrophil migration and enhanced macrophage phagocytosis at nanogram concentrations[202]. MaR1 was recently used in a DSS and TNBS-induced colitis model in mice. Alle*via*tion of disease activity index, loss of body weight and tissue damage in the colon, along with a significant decrease in the levels of inflammatory cytokines was reported, most likely through the inhibition of the NF-κB pathway. In the same study, a reduction in the migration of neutrophils, ROS production and inflammatory cytokines in LPS-stimulated bone marrow-derived macrophage cultures incubated with MaR1 was reported[206].

**CONCLUSION**

There is no doubt that eicosanoids are an important family of immunoregulatory bioactive lipids with strong implications for both promotion and prevention of colon cancer. During inflammation, many of these autacoids act antagonistically or synergistically; frequently in a temporal manner involving different cell types in order to bring about homeostasis. Many of these bioactive lipids are also essential for various cellular functions. Despite its importance, very few therapeutic options are available that can modulate the aberrant production of these molecules specifically in the context of colorectal or other cancers. ASA is undoubtedly one of the best known drugs that can interfere with the COX pathway; however, ASA needs to be consumed long term (at least 5 years) in order to observe any protection from cancer. Use of ASA is also associated with significant bleeding events and is thus not suitable universally. COX-2 inhibitors, that specifically target the inflammatory arm of the COX metabolism pathway, are approved primarily for pain relief rather than for cancer chemotherapy and are also associated with significant cardiovascular side effects. On the other hand, CysLTR antagonists that were designed for asthma have not had widespread proven efficacy either[207]. Since inhibition of one pathway leads to the activation of another due to the shunting of the substrates, combined COX/LOX inhibitors have proved to be more effective and need to be explored further in the context of CRC.

The identification of a ‘druggable’ target in the generation of eicosanoids is necessary, with a concerted effort from the scientific community to develop drugs that are specifically effective in cancer. Perhaps the greatest promise comes from the newly discovered resolution mediators such as lipoxins, resolvins and mareisins; early studies indicate that these mediators are effective at very low concentrations. Therefore, the efficacy of these compounds as viable chemopreventive/therapeutic options in CRC may be anticipated.

It is also interesting to note that COX-2 or 5-LOX that are associated with pro-carcinogenic events or 15LOX-1, which is associated with anti-carcinogenic events in CRC, rarely show any mutations. Deregulation in their activity comes from their overexpression, enhanced enzymatic activity or epigenetic silencing. Therefore one may envisage the design and development of chromatin modifiers that can reduce the expression of the pro-inflammatory enzymes such as COX-2 or 5-LOX while enhancing the expression of the anti-inflammatory enzymes such as 15-LOX-1.

There is no dearth of information in the literature and clinical trials highlighting the importance of eicosanoids in cancer. Delving into the details of how the eicosanoids function both in the tumor as well as in the stromal cells will be essential to understand the pathways involved, which will, in turn aid in the design of novel cancer therapies.

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**Figure 1 Enzymatic metabolism of polyunsaturated fatty acid can generate bioactive lipids that induce inflammation, tumorigenesis and thrombosis while also generating mediators with anti-tumorigenic, pro-resolution properties.** In the pro-tumorigenic arm, arachidonic acid (AA) can be metabolized through the cyclooxygenase (COX) pathway to generate prostaglandins (PGE2, PGI2) and thromboxanes (TxA2). The lipoxygenase (LOX) enzymes can convert AA to hydroxyeicosatetraenoic acids (HETEs), which are active on their own, or can be further converted to leukotriences (LTs). In the anti-tumorigenic, pro-resolution arm, the metabolism of AA through 15-LOX1/2 or acetyl salicylic acid (ASA) acetylated COX-2 generates intermediates that can be converted to lipoxins (Lxs) through the transcellular activity of other LOXs (5- or 12-LOX). Conversion of linoleic acid (LA) to 13(S)-HODE may have anti-inflammatory functions through the activation of PPARγ. Fish oils eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be converted by acetylated COX-2 to the pro-resolution mediators E- and D- series resolvins (Rvs), respectively. PUFA: Polyunsaturated fatty acid.

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**Figure 2 The activation of PPARγ through bioactive lipids can modulate signaling in the progression of colorectal cancer.** 15-deoxy-delta(12,14)-prostaglandin J2 (15-PGJ2), generated from arachidonic acid (AA) through the enzymatic action of COX-2 acts as a ligand for PPARγ. Along with co-activators such as RXR activation of tumor suppressive signaling through Kruppel like factor 4 (KLF4) in colorectal cancer (CRC) has been reported. Binding to co-repressors may lead to the repression of various transcription factors such as nuclear factor kappa B (NF-κB), AP1 (Activator Protein-1, c-Jun and c-Fos), c-Myc or STAT. 13(S)-hydroxyoctadecadienoic acid [13(S)-HODE], generated through the oxygenation of linoleic acid (LA) by 15-LOX-1, can act as a ligand for PPARγ and lead to inhibition of NF-κB activity. 13(S)-HODE may also inhibit the transcriptional activity of PPARβ/δ and STAT3, thereby reducing inflammation and angiogenesis in CRC.