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TOPIC HIGHLIGHT

2015 Advances in Colorectal Cancer

Eicosanoid pathway in colorectal cancer: Recent updates

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Abstract

Enzymatic metabolism of the 20C polyunsaturated fatty acid (PUFA) arachidonic acid (AA) occurs *via* the cyclooxygenase (COX) and lipoxygenase (LOX) pathways, and leads to the production of various bioactive lipids termed eicosanoids. These eicosanoids have a variety of functions, including stimulation of homeostatic responses in the cardiovascular system, induction and resolution of inflammation, and modulation of immune responses against diseases associated with chronic inflammation, such as cancer. Because chronic inflammation is essential for the development of colorectal cancer (CRC), it is not surprising that many eicosanoids are implicated in CRC. Oftentimes, these autacoids work in an antagonistic and highly temporal manner in inflammation; therefore, inhibition of the pro-inflammatory COX-2 or 5-LOX enzymes may subsequently inhibit the formation of their essential products, or shunt substrates from one pathway to another, leading to undesirable side-effects. A better understanding of these different enzymes and their products is essential not only for understanding the importance of eicosanoids, but also for designing more effective drugs that solely target the inflammatory molecules found in both chronic inflammation and cancer. In this review, we have evaluated the cancer promoting and anti-cancer roles of different eicosanoids in CRC, and highlighted the most recent literature which describes how those molecules affect not only tumor tissue, but also the tumor microenvironment. Additionally, we have attempted to delineate the roles that eicosanoids with opposing functions play in neoplastic transformation in CRC through their effects on proliferation, apoptosis, motility, metastasis, and angiogenesis.

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

Core tip: Eicosanoids are bioactive lipids 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 to regulate some of the most important steps in the development of acute

inflammation and its resolution. Aberrant expression of the enzymes that help synthesize these bioactive lipids is frequently seen in diseases associated with chronic inflammation, including cancer.

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INFLAMMATION AND COLORECTAL CANCER

Tumors show characteristics of inflamed tissue, including the presence of immune cells within the tumor tissue[1]. Although the presence of leukocytes within tumors was initially thought to result from 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, immune cells that invade the local tumor microenvironment are phenotypically different from normal immune cells, and can maintain the inflammatory milieu and promote invasion and migration of the transformed epithelial cells[3].

Colorectal carcinoma (CRC) is one of the best examples of an inflammation-associated cancer[4]. During colorectal carcinogenesis, epithelial cells in the colon accumulate mutations, which lead to either inactivation or activation of certain target genes that provide a selective growth advantage. In turn, this results in the transformation of normal epithelium to an 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, when compared with the general population, epidemiological studies have shown a higher incidence of CRC in patients with a previous history of inflammatory bowel disease (IBD)[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 mortality from sporadic CRC and suppresses adenoma growth in patients with familial adenomatous polyposis (FAP) and who inherit a mutation in the tumor suppressor APC gene[6]. Similar to other solid malignancies, pathological examinations of CRC tissue reveal the presence of innate immune cells, including neutrophils, mast cells, natural killer cells, and dendritic cells that are recruited to the tumor and suppress tumor growth and angiogenesis[7]. This phenomenon is called immune-surveillance, and assists in the early detection and elimination of transformed cells and preneoplastic aberrant crypt foci (ACF), which may progress to 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 a 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 (PUFAs) are among the earliest signaling molecules released in response to an injury or inflammatory stimulus. The role played by these small mediators in inflammation and its resolution has garnered a great amount of recent interest[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 termed eicosanoids. AA is also known as an n-6 fatty acid, signifying the position of the carbon with the first double bond when considering the terminal methylene carbon group as the first carbon. AA is derived from linoleic acid (LA, 18:2n-6), an 18C essential fatty acid, through the subsequent actions of desaturases and elongases located primarily in the liver. The release of AA from phospholipids in the outer nuclear membrane is achieved through the activity of phospholipases such as the calcium-dependent cytosolic phospholipase A_2 ($cPLA_2$). After being released, the free fatty acid can be metabolized *via* enzymatic pathways including the cyclooxygenase (COX) and lipoxygenase (LOX) pathways to generate 2-series prostaglandins (PGs) and thromboxanes (Txs) (COX pathway) or 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 a variety of 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]. As these fatty acids are primarily obtained through the diet, increased consumption of fish oil can alter the fatty acid profiles of the plasma and cell membranes in a time and dose-dependent manner[15], primarily at the

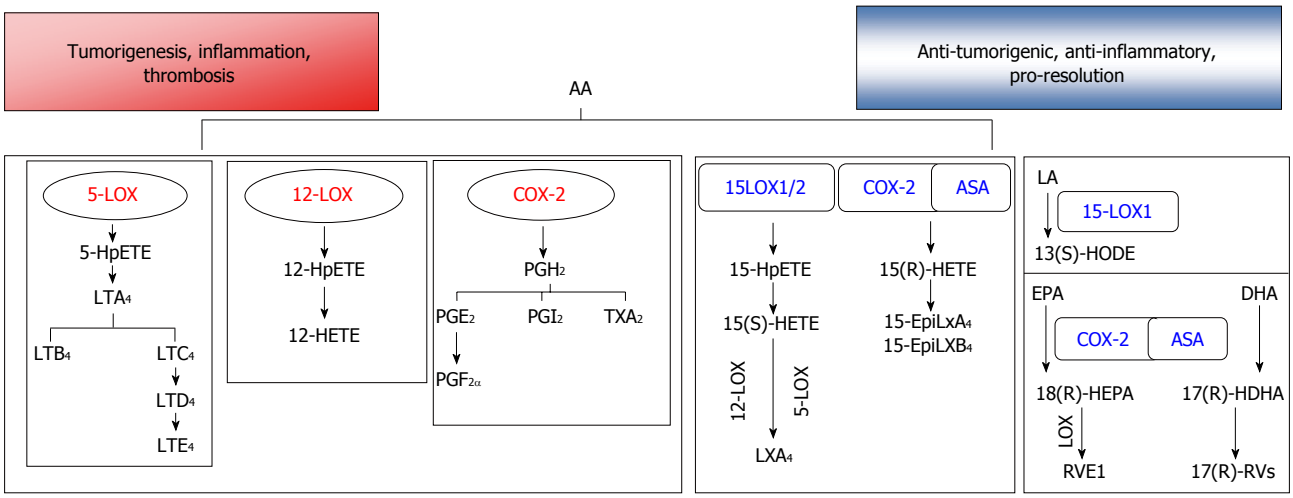

Figure 1 Enzymatic metabolism of polyunsaturated fatty acid can generate bioactive lipids that induce inflammation, tumorigenesis, and thrombosis, while also generating mediators with anti-tumorigenic, pro-resolution properties. In the pro-tumorigenic arm, arachidonic acid (AA) is metabolized *via* the cyclooxygenase (COX) pathway to generate prostaglandins (PGE_2, PGI_2) and thromboxanes (TxA_2). Lipoxygenase (LOX) enzymes convert AA to hydroxyeicosatetraenoic acids (HETEs), which are active on their own, or can be further converted to leukotrienes (LTs). In the anti-tumorigenic, pro-resolution arm, 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 produce anti-inflammatory effects mediated through activation of PPARγ. The fish oils eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be converted by acetylated COX-2 to pro-resolution mediators E- and D-series resolvins (Rvs), respectively. PUFA: Polyunsaturated fatty acid.

expense of AA. This implies a decreased production of inflammatory AA-derived eicosanoids, which has been verified in healthy human volunteers who showed decreased levels of PGs and LTs after consuming EPA and DHA supplements for varying lengths of time[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 are readily recognized by PG and LT receptors, and are therefore considerably less potent in inducing inflammation[17]. Both EPA and DHA are substrates for the production of 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 *via* several different mechanisms that include, but are not limited to, induction of inflammation, regulation of cellular oxidative stress, activation of receptors involved in cellular signaling pathways, and the alteration of membrane dynamics[19].

COX-2-derived lipid mediators

AA is metabolized to prostaglandins either by 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 produced from AA (PGH_2) can be further metabolized to a several other prostaglandins; among which, PGE_2 has been strongly implicated in the development of gastrointestinal tumors[22]. This prostanoid acts *via* four G-protein coupled receptors (EP_{1-4}) and can enhance tumorigenesis through a variety of mechanisms, including enhanced cell proliferation, suppression of apoptosis, and induction of angiogenesis[23].

Elevated levels of COX-2 and an accompanying elevation of PGE_2 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, and that these interactions contribute to cancer progression. PGE_2 modulates cancer-associated immune suppression by recruiting T cells, $CD8^+$ cytotoxic T cells, regulatory T cells, dendritic cells, and myeloid-derived suppressor cells (MDSCs)[20]. Additionally, secretion of PGE_2 may enhance oxidative stress, leading to a state of low grade continuous inflammation characterized by the infiltration of neutrophils and macrophages, and eventually leading to mitogenic signaling[18]. PGE_2 has been shown to stimulate macrophages to produce pro-inflammatory chemokines and cytokines, such as macrophage chemoattractant protein-1 (MCP-1), which recruits leukocytes from the circulation to local sites of inflammation[25]. A previous study[26] showed that MCP-1 levels were higher in intestinal epithelial cells, and that MCP-1 could stimulate COX-2 expression as well as the release of PGE_2 and vascular endothelial growth factor (VEGF) in human macrophages.

In the adaptive response, PGE_2 mediated signaling may affect cytokine production in antigen-presenting

cells by influencing the functional phenotype of T cells [*i.e.*, by switching 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, PGE_2 was shown to worsen inflammation and disease severity by increasing neutrophil and Th17 cell infiltration into colonic tissue[29]. Furthermore, PGE_2 was shown to amplify IL-23-mediated Th17 cell expansion by acting on its receptor (EP_4) located on T cells and dendritic cells[30].

The pro-tumorigenic effects of PGE_2 may also be mediated by T_{reg} cells, which contribute to immune evasion by tumor cells in a variety of cancers. Increased COX-2 expression and elevated PGE_2 production in adaptive FoxP3-positive T_{reg} cells found within tumors and mesenteric lymph nodes have been shown to contribute to an immunosuppressive microenvironment in CRC. This type of microenvironment facilitates tumor growth by suppressing effector T cells and inducing resistance to antigen-specific cancer immunotherapy[31,32]. A role for COX-2 in tumor immunity was also exhibited in COX-2 expressing colon cancer cell lines, where expression of FasL and TRAIL was shown to cause a counter-attack against cytotoxic T cells[33].

COX-2 overexpression is frequently associated with the concomitant expression of microsomal PGE synthase-1 (mPGES-1), the terminal synthase that leads to the preferential production of PGE_2[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 aberrant crypt foci (ACF) in a carcinogen-induced colon cancer model[35]. Together, these findings suggest that mPGES-1 plays crucial roles during colon cancer progression, and that these roles are relevant to the promotion of inflammation. Thus targeting mPGES-1 may be a feasible option for cancer chemoprevention[36].

Interestingly, prostaglandins are also essential for the health of gastrointestinal mucosa by maintaining mucosal integrity, promoting wound healing, and limiting inflammation[36]. The absence of $cPLA_2$ in mice was recently shown to globally reduce the formation of AA-derived bioactive lipids, increase mucosal ulceration, and increase the expression of pro-inflammatory cytokines[34]. Mice with a targeted deletion of COX-2 in their endothelial cells and myeloid cells and treated with dextran sulfate sodium (DSS) displayed greater weight loss and had worse clinical scores compared to their WT littermates. However, mice with a targeted deletion of COX-2 in their colonic epithelial cells were not susceptible to DSS[37]. Additionally, mPGES-$1^{-/-}$ mice were recently reported to show more extensive inflammation in the GI tract when compared with WT mice[34]. This could have resulted from a shift in the metabolism of prostaglandins; *e.g.*, a loss of PGE_2 was associated with a gain in PGD_2, 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 PGE_2) by hydroxyprostaglandin dehydrogenase 15-(NAD) (15-PGDH) can regulate the availability and efficacy of prostanoids[20]. In fact, 15-PGDH is frequently down-regulated in a variety of cancers, suggesting its tumor-suppressive role[11]. Overexpression of 15-PGDH in colon cancer cells was shown to strongly inhibit 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 PGE_2 levels, which may allow cancer cells to escape immune surveillance.

Randomized clinical trials and observational studies have indicated that long-term use ($\geqslant$ 5 years) of acetyl salicylic acid (ASA, Aspirin®), which inhibits both COX-1 and COX-2, leads to significant reductions in the risks for developing colorectal, esophageal, gastric, biliary, and breast cancer, as well as their distant metastases[41]. Furthermore, the daily use of ASA has been reported to specifically prevent the development of colorectal polyps and reduce the risk for developing sporadic CRC or CRC from Lynch syndrome[42-44]. Moreover, the use of ASA after a diagnosis of CRC can also improve survival, and 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 reported reduced cancer recurrence and mortality[45]. Moreover, ASA use was associated with a greater reduction in the risk for developing colorectal tumors when the normal colonic mucosa showed a higher expression of 15-PGDH[45].

Other prostaglandins produced in the eicosanoid pathway, such as PGD_2, have 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 PGD_2 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 that selective modulation of these mediators may prevent tumor growth in CRC.

LOX-derived lipid mediators

PUFAs are oxygenated *via* the enzymatic action of LOXs to form LTs and hydroxyeicosatetraenoic acids (HETEs), which both 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], and are named according to the position of the carbon atom in

AA that these enzymes oxygenate. Except for *ALOX5*, which is located on chromosome 10, most of the other LOX genes are located within a few megabases of each other on the short arm of chromosome 17[13]. Although AA is the preferred substrate for oxygenation for most LOXs, some LOX 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, and especially in leukocytes[51]. This enzyme catalyzes the conversion of AA to 5S-hydroperoxyeicosatetraenoic acid (5-HpETE), and its subsequent conversion to LTA_4. LTA_4 can be converted to LTB_4 and then to cysteinyl leukotrienes by the actions of LTA_4 hydrolase and LTC_4, synthase, respectively[52] (Figure 1). 5-LOX activity is exquisitely sensitive to various stimuli, including the second messenger Ca^{2+}. Ca^{2+} can bind to the N-terminus of 5-LOX, which contains a hydrophobic domain and facilitates the binding of 5-LOX to membrane phospholipids[53]. The 5-LOX enzyme is usually located in the cytoplasm as a soluble protein; however, in the presence of Ca^{2+}, it may become phosphorylated and translocate to the nuclear or endoplasmic reticulum (ER) membrane, where with the help of 5-LOX activating protein (FLAP), it catalyzes the oxygenation of AA[53]. Therefore, many stimuli that increase the levels of intracellular calcium ions (*e.g.,* antigens, microbes, cytokines, and toxins) can induce the production of LTs[53,54].

LTs are classified into two general categories: LTB_4 and cysteinyl LTs (LTC_4, LTD_4, and LTE_4)[55]. LTs play key roles in the pathogenesis of inflammatory disorders, including IBD, and typically stimulate quick and short-lasting events (*e.g.,* smooth muscle contraction, 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 LTB_4, and CysLT1/2 and GPR17 for the Cys-LTs[52,56].

5-LOX is overexpressed in tissues with chronic inflammation and also in transformed cells. 5-LOX was shown to be up-regulated in patients with polyps and colon cancer[57], whereas in the $APC^{\Delta 468}$ mouse model of polyposis, the loss of 5-LOX was protective[58]. In the same model, 5-LOX metabolic products produced by hematopoietic cells were shown to promote tumorigenesis by enhancing both the proliferation of intestinal epithelial cells and recruitment of MDSCs to the spleen, mesenteric lymph nodes, and primary tumor[59]. Dietary administration of a 5-LOX inhibitor (Zileuton) to $APC^{\Delta 468}$ mice resulted in overall reductions in systemic inflammation, polyp number, and inflammatory infiltration into lesions[59].

Overproduction of LTB_4 in human colon cancer tissue is implicated in the pathogenesis of IBD. Additionally, high expression of the LTB_4 receptor BLT1 has been detected in human colon tissues[60]. These findings indicate the importance of an inflammatory autocrine loop during the promotion and progression phases of colon tumors. The inflammatory mediators can cause intestinal epithelial cells to up-regulate their expression of enzymes needed for the biosynthesis of eicosanoids, including the CysLTs, and signal transducing CysLT receptors, to provide a self-sufficient signaling mechanism needed to maintain both inflammation and tumor progression[58]. Taken together, these studies show that pro-inflammatory LTs might facilitate tumor growth by establishing an inflammatory microenvironment.

Metabolism of AA by 12-lipoxygenase (12-LOX) leads to the production of 12-HETE, which has been shown to stimulate the growth of various cancers[61]. Additionally, a $Gln^{261}Arg$ polymorphism in the *ALOX12* gene was shown to be associated with an enhanced susceptibility to several malignancies, which also indicates a potential oncogenic role for 12-LOX[62,63]. Although a recent meta-analysis of studies with 8379 subjects revealed that this specific polymorphism was not associated with an increased risk of colon cancer[64], other studies have reported 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 associated with inflammation[61]. Moreover, 12-LOX expressing colon cancer cell lines have demonstrated increased migration as a result of decreased E-cadherin and integrin-β1 expression[61], or enhanced production of reactive oxygen species (ROS) and activation of the catalytic subunit of the NADPH oxidase complex, Nox1[65].

Unlike 5-LOX and 12-LOX, 15-lipoxygenase-1 (15-LOX-1), which can oxygenate AA and LA as well as complex substrates such as biomembranes[66], 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 shown that 13(S)-HODE was the only metabolite that significantly increased in the Caco-2 model of cellular differentiation[67,68]. Additionally, an assay of > 120 cancer cell lines from 20 different cancer types indicated an almost universal loss of 15-LOX-1 expression in de-differentiated cell lines when compared with well-differentiated cancer cells or non-transformed cells[68]. Moreover, levels of 13(S)-HODE were shown to be reduced in colorectal polyp samples obtained from patients suffering from FAP when compared to their levels in paired normal tissues[67]. A loss of 15-LOX-1 expression is primarily due to epigenetic factors, such as nucleosomal remodeling and the histone deacetylase (NuRD) complex[69]. Re-expression of 15-LOX-1 has been achieved *via* routes including histone methylation/demethylation, acetylation[70,71] or the 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 15-LOX-1 expression was lower in samples of tumor tissue compared to normal tissue[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 has resulted in lower levels of TNFα and inducible nitric oxide synthase (iNOS) in epithelial cells[73]. In human CRC, down-regulation of 15-LOX-1 was associated with increased IL-1β expression[74]. This was 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 was re-expressed in the gut[73,75,76]. Additionally, there is 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 is efficiently oxygenated by 15-LOX-1 to produce 13(S)-HODE, AA can also be metabolized by both 15-LOX-1 and 15-LOX-2 to produce 15(S)-HETE[78]. 15(S)-HETE levels were reported to be significantly lower in the serum of colorectal cancer patients when compared to their levels in control subjects[78].

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

EICOSANOIDS AND THE HALLMARKS OF CANCER

Various types of cancer cells and surrounding stromal cells produce high amounts of pro-inflammatory eicosanoids. These bioactive lipid metabolites can modulate tumor progression through several mechanisms, including directly activating receptors on tumor epithelial cells that help regulate cell proliferation, apoptosis, migration, and invasion, and inducing epithelial cells to secrete growth factors, pro-inflammatory mediators, and angiogenic factors. All of these molecules can facilitate tumor growth, and also support tumor-associated angiogenesis and evasion of the immune system[20].

Proliferation and apoptosis

It is already well documented that tumor growth relies on a deregulated balance between cellular proliferation and cell death. It is not surprising that various eicosanoids that 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 50%-80% of all colorectal cancers[79]. At the cellular level, COX-2 overexpression was shown to increase cell-to-matrix adhesion and inhibit apoptosis in human CRC cells[80-82]. Furthermore, in the $APC^{\Delta 716}$ 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 size of adenomatous colonic polyps in patients with FAP[84]. Additionally, conventional NSAIDs are known to inhibit chemically-induced colon cancer in rodent models by inhibiting COX-2 activity[85]. In the human colon cancer cell line HCT-116, COX-2 was induced through wild-type p53-mediated activation of the Ras/Raf/ERK cascade, which subsequently blocked p53 or genotoxic stress-mediated apoptosis. This anti-apoptotic effect may represent a mechanism for diminishing cellular stress associated with p53 induction[86]. On the other hand, NSAIDs inhibited expression of the anti-apoptotic protein Bcl-X_L, resulting in an altered BAX to Bcl-X_L ratio and enhanced apoptosis[87]. Increased expression of the anti-apoptotic protein Bcl-2 and reduced expression of the pro-apoptotic protein Bim caused by the COX-2-derived eicosanoid PGE_2 have also been reported[21,88].

A considerable amount of crosstalk has been reported between the COX-2 and EGFR pathways. For instance, PGE_2 treatment was shown to significantly increase cellular proliferation and reduce apoptosis in a rodent CAC model[89], and also induce COX-2 expression in intestinal adenomas by activating the MAPK signaling pathway[90]. PGE_2 was shown to induce ERK2 signaling in colon cancer cell lines by stimulating the rapid phosphorylation of EGFR[91]. Inhibition of both EGFR and COX-2 achieved by using 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] reported that during glucose deprivation, PGE_2 can promote tumor cell survival in the colon by activating the PI3K/AKT pathway, which in turn may up-regulate COX-2 and down-regulate 15-PGDH. Moreover, glucose deprivation was also demonstrated to activate the unfolded protein response (UPR), resulting in elevated expression of the C/EBP-homologous protein (CHOP), which was positively correlated with 15-PGDH expression. These data suggest that stress conditions can regulate PGE_2 as a common and crucial mediator of cell survival during adaptation to the tumor microenvironment.

In the colorectal adenocarcinoma cell line DLD-1, PGE_2 was shown to bind to EP_2, which stimulated tumor growth by activating PI-3K/AKT signaling,

followed by activation of the β-catenin signaling pathway[94]. PGE_2 can also induce cell proliferation in colorectal tumors through the EP_4 receptor by inducing phosphorylation of ERK[95]. Additionally, Park *et al*[96] have proposed that COX-2 inhibition may produce significant anti-tumorigenic effects by blocking stroma-derived PGs. These authors used a co-culture model to evaluate cancer cell-stromal cell relationships and reported that use of an EP_4 antagonist resulted in decreased proliferation in the COX-2 non-expressing LS174T colon adenocarcinoma cell line.

In contrast to PGE_2, 15d-PGJ_2 was shown to induce apoptosis[97] and cell cycle arrest in CRC cells[98] by inhibiting activity of the inflammatory transcription factor NF-κB, reducing the levels of anti-apoptotic genes[97], down-regulating c-Myc expression, and upregulating c-Jun and GADD153[99]. When 15d-PGJ_2 and histone deacetylase (HDAC) inhibitors were added in combination to colon cancer cell lines, they exerted a synergistic effect on caspase-dependent apoptosis, leading to ROS generation, ER stress, decreased expression of anti-apoptotic proteins Bcl-X_L and XIAP, and increased expression of CHOP and DR5 (Death receptor 5, TRAIL-R2). Furthermore, the same effects of this co-treatment were also seen *in vivo*, with an inhibition in tumor growth in a nude mouse xenograft model inoculated with DLD-1 cells[100]. Shin *et al*[101] suggested that the growth inhibition and 15d-PGJ_2-induced apoptosis seen in human and murine CRC cell lines were caused by ROS dependent down-regulation of AKT and p-AKT.

LOX pathways in proliferation and apoptosis

The 5-LOX protein is overexpressed in the early stages of colon cancer, where its expression is significantly correlated with patient age, polyp size, and the presence of 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 proliferation in a colon cancer cell line and reduce the size of xenografted tumors[57]. LTB_4 demonstrated pro-carcinogenic effects in CRC by activating the ERK pathway[103]. Induction and/or accumulation of COX-2, β-catenin, and Bcl-2, as well as PGE_2 production in non-transformed epithelial linings in the colon have also been reported in the presence of LTB_4[104]. Furthermore, LTD_4, a cysteinyl leukotriene, was reported to inhibit caspase 3, and thereby increase 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 amount of COX-2 metabolites produced by inflammatory cells, indicating that inhibition of one pathway could shunt metabolism of AA towards the other pathway[107-109]. Dual inhibition of 5-LOX and COX-2 may produce 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]. Gaining a 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 conducted in the past several years have revealed an unequivocal tumor suppressive role for 15-LOX-1 in CRC[113]. While initial studies indicated an anti-apoptotic role for the enzyme, those investigations were primarily conducted using inhibitors such as NDGA (nordihydroguaiaretic acid), which may have pleiotropic effects in cells[114]. Yoshinaga *et al*[115] reported that 15-LOX-1 over-expression in colon cancer cell lines increased cell proliferation *via* activation of ERK, followed by a decrease in $p21^{(Cip/WAF1)}$ expression. However, numerous 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, both 15-LOX-1 expression and levels of 13(S)-HODE were reduced in the polyps when compared to paired normal tissues obtained from patients with FAP[67]. 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. Therefore a transgenic mouse model was established that can express human 15-LOX-1 specifically in gut epithelial cells[74]. These mice showed a decreased incidence of tumors[73]. Interestingly, an inverse correlation between 15-LOX-1 and COX-2 expression has been proposed to occur during the adenoma to carcinoma sequelae[118], leading to the accumulation of pro-tumorigenic PGs and the loss of 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 progressive CRC may lead to an increase in COX-2 expression, and thus exacerbate the inflammatory milieu[119].

However, focusing on the effects of 15-LOX-1 expression only in epithelial intestinal cells may not provide sufficient information about how its expression contributes to CRC development. Additional knowledge concerning the effects of 15-LOX-1 and its metabolites on tumor-associated stromal cells and endothelial cells is also required to understand the underlying mechanisms of CRC development that lie beyond 15-LOX-1 signaling.

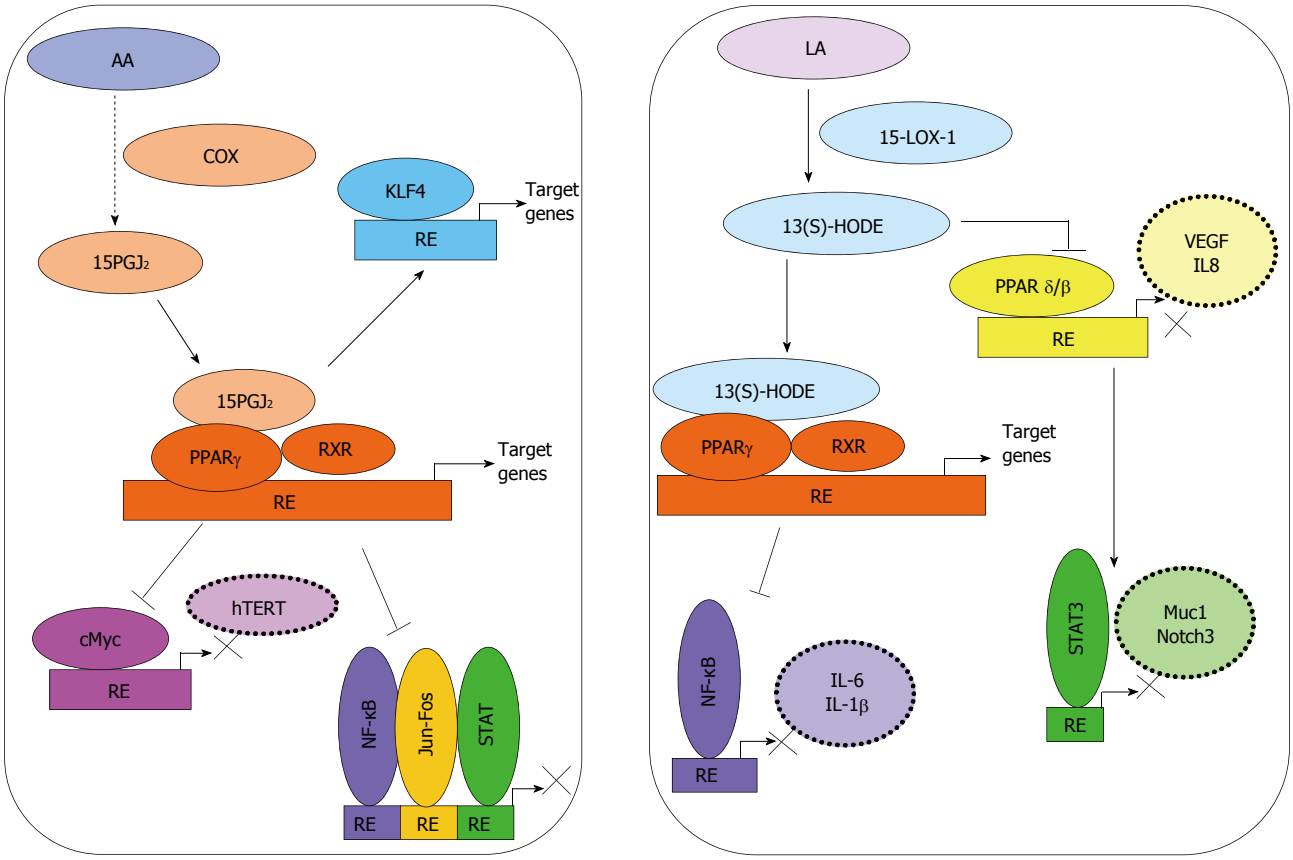

Figure 2 Activation of PPARγ by bioactive lipids can modulate signaling in progressive colorectal cancer. 15-deoxy-delta(12,14)-prostaglandin J2 (15-PGJ2), generated from arachidonic acid (AA) by the enzymatic action of COX-2, acts as a ligand for PPARγ. Co-activators such as RXR activation of tumor suppressive signaling through Kruppel-like factor 4 (KLF4) in colorectal cancer (CRC) have also been reported. Binding to co-repressors may lead to 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 by 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 activities of PPARβ/δ and STAT3, and thereby reduce inflammation and angiogenesis in CRC.

NF-κB and PPAR signaling pathways driven by eicosanoids in CRC

In colon cancer, the activity of NF-κB in intestinal epithelial cells and myeloid cells in the tumor environment plays 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 a nuclear hormone receptor superfamily that includes PPARα, PPARγ, and PPARβ/δ. Each of these receptors can mediate the physiological actions of numerous fatty acids and fatty acid-derived molecules that serve 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 normal colon tissue, and show 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 ACF in rats[124]. On the other hand, PPARβ/δ is associated with pro-inflammatory pathways and progression of CRC[121].

15d-PGJ2, a natural agonist of PPARγ, was shown to inhibit the proliferation of HT-29 human colon cancer cells by up-regulating 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 of Caco-2 CRC cells by repressing telomerase activity and telomerase reverse transcriptase (hTERT) expression by down-regulating c-Myc and up-regulating 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, and thereby promote induction of endogenous PPARγ target genes related to induction of apoptosis[128]. In support of this finding, over-expression of 15-LOX-1 was associated with decreased proliferation and increased apoptosis, as well as reduced cellular motility, anchorage-independent growth, migration, and cell invasion in colon cancer cells[118]. Moreover, increased 13(S)-HODE-mediated PPARγ activation has been suggested to inhibit activation of NF-κB, which is associated with decreased cell viability[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 by inhibiting NF-κB[130,131].

13-(S)HODE has been shown to suppress PPAR-δ; a receptor that can transcriptionally upregulate IL-6 expression, and thereby promote colitis and CAC[128,132,133]. Very recently, 15-LOX-1-induced inhibition of PPARδ during promotion of CAC was shown to be mediated by suppression of IL-6 expression, STAT3 phosphorylation, and Notch3 expression[134]. Moreover, elevated expression of PPARδ has been implicated in the pathogenesis of CRC[135,136], and a positive correlation between PPARδ expression and the late stages of CRC has also been observed[137]. PGI_2 was shown to activate PPARδ, which may lead to a loss of apoptosis through sequestering of the pro-apoptotic protein BAD by 14-3-3 epsilon and reduced mitochondrial damage[138]. Similarly, stromal PGI_2 generation was claimed to promote cell survival in colonocytes by activating PPARδ[139]. More recently, PPARδ activation was also associated with an increased expression of VEGF and IL-18 in colon cancer cells, through p300 and the PI3K/AKT pathway. Furthermore, hypoxia stimulated PPARδ activation enhanced angiogenesis, macrophage recruitment, and macrophage proliferation in the tumor microenvironment[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]. These findings suggest 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 several factors expressed/released not only by tumor cells, but also by stromal cells. PGE_2 is claimed to promote a more metastatic CRC phenotype[146]. An analysis of sporadic colorectal adenocarcinoma tissue samples revealed a significant relationship between COX-2-derived PGE_2 levels and tumor stage: higher PGE_2 levels were reported in metastatic tumor specimens when compared to tumor specimens without metastases. Thus, it can be concluded that PGE_2 levels may be correlated with tumor aggressiveness, its ability to metastasize, and patient prognosis[147].

Epidemiological, clinical, and animal studies have demonstrated that COX-2 and epidermal growth factor (EGF) signaling pathways coordinate their activities to play key roles in promoting CRC growth and metastasis[148]. For example, EGFR expression was directly correlated with the potential of human CRC cells to metastasize to the liver[149]. Moreover, Buchanan *et al*[150] suggested that in early stage CRC, the initial effects of PGE_2 were mediated by EGFR transactivation and subsequent phosphorylation, which was also responsible for down-stream effects, including cell migration and invasion. In their following reports, the same group showed that PGE_2 activated an EP_4/β-arrestin1/c-Src signaling complex, resulting in EGFR transactivation and downstream Akt signaling, which subsequently stimulated migration of CRC cells *in vitro* as well as their metastatic spread to the liver *in vivo*[151]. Additionally, in the presence of functional EGFR, PGE_2 was shown to transactivate hepatocyte growth factor receptor (c-Met-R), and thereby increase phosphorylation and accumulation of the oncogene β-catenin. This sequence of events induced expression of urokinase-type plasminogen activator receptor (uPAR), resulting in increased CRC cell invasiveness[152]. A significant decrease in liver metastasis with the use of selective EP_4 receptor antagonists has also been reported[153]. In another report, PGE_2 treatment was shown to activate JNK1/2 kinase. This activation was followed by an increase in the levels of migration-related factors uPA and MMP-9, which further promoted cellular motility in the human colon cancer cell line LoVo. However, pretreatment with 17β-estradiol down-regulated uPA and MMP-9 expression *via* deactivation of JNK1/2, and inhibited PGE_2-induced LoVo cell motility. Based on these findings, the authors suggested that the incidence and mortality rates of CRC in women were lower than those in men because estrogen helps protect against development of fatal colon cancer, and thus reduces mortality from this disease[154].

In contrast to PGE_2, PGI_2 is known for its anti-metastatic effects in CRC. PGI_2 analogues have been 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 concerning the roles of LOX enzymes in colon cancer migration and invasion have recently been reported[156]. In one study, decreased levels of the selective LOX inhibitor, NDGA, were found in mobile human colon cancer cells; this was partly explained by inhibition of MMP-2 and MMP-9[157]. Loss of 15-LOX-1 expression was found in the 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, as well as angiogenesis, cancer cell migration, and invasion.

Angiogenesis

For tumors to grow and metastasize, they must 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 needed for proliferation, migration, capillary tube formation, and recruitment of endothelial cells[160]. Numerous *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 stabilization of transcription factor HIF-1α, which activates genes which have the hypoxia-responsive element (HRE) in their promoter region, such as *VEGF*. VEGF exerts its effects on target cells through tyrosine kinase receptors, including VEGF receptors 1 (VEGFR1, Flt1) and 2 (VEGFR-2, Flk-1/KDR)[161]. Ligand binding induces receptor dimerization and activation of downstream signaling pathways including the MAPK family, PI3K/AKT and 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 various lipid mediators such as PGE_2[165-168].

COX pathway in angiogenesis

PGE_2 stimulation has been shown to induce HIF-1α stabilization[163] and VEGF expression *in vitro*[169]. Additionally, VEGF and COX-2 expression and tumor angiogenesis were shown to be highly correlated in samples of colon cancer tissue[147,170]. Through its receptor EP_2, PGE_2 was shown to stimulate the nuclear translocation of β-catenin[94], whereby it activated T cell factor 4 (TCF-4) and HIF-1α to trigger cell survival, proliferation, and angiogenesis in colon cancer[171,172]. Homozygous knock-out of EP_2 completely abrogated induction of VEGF in the intestinal polyp stroma of $APC^{\Delta 716}$ mice. It also decreased the number and size of intestinal polyps, showing that PGE_2-directed induction of VEGF was an important factor for tumor growth[173]. Moreover, PGE_2 was shown to induce expression and release of the pro-angiogenic chemokine CXCL1 in CRC, which in turn stimulated microvascular endothelial cell migration and tube formation both *in vitro* and *in vivo*[174]. Hypoxia was shown to induce EP_1 expression in colon cancer cells, while inactivation of EP_1 inhibited PGE_2-dependent and hypoxia-inducible expression of angiopoietin-like protein 4 (ANGPTL4), whose lipid metabolizing functions are exerted *via* inhibition of lipoprotein lipase (LPL)[175].

In addition to inducing several angiogenic factors in epithelial cells, PG signaling in surrounding stromal cells also supports angiogenesis in colon cancer. For example, PGE_2 and TXA_2 were reported to regulate the adhesion and spreading of human umbilical vein endothelial cells (HUVEC) through cAMP-dependent activation of protein kinase A (PKA) and cAMP- and PKA-dependent activation of Rac, respectively[176]. Besides VEGF, PGE_2 may also mediate the angiogenic effects of basic fibroblast growth factor (bFGF) by up-regulating expression of 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]. TXA_2 has been shown to enhance endothelial cell migration and angiogenesis[178]. An increase in TXA_2 levels, as a result of overexpression of TXA_2 synthase in C-26 colon adenocarcinoma cells allografted to BALB/c mice, was reported to stimulate accelerated tumor growth and tumor-associated angiogenesis[179].

The process of angiogenesis may require not only crosstalk between tumor epithelial and endothelial cells, but also the involvement of immune cells that produce pro-angiogenic factors. PGE_2 has been shown to induce mast cells to release VEGF and the chemokine CCL2[180,181], which can induce tumor-associated angiogenesis by directly recruiting CCR2 expressing endothelial cells and inducing VEGF release from macrophages[26]. Contrary to the pro-angiogenic roles described above, PGE_2, through its receptor EP_2, was shown to inhibit secretion of VEGF in Caco-2 colon cancer cells exposed to hyperosmotic stress[182]. Additionally, 15d-PGJ_2 was shown to down-regulate COX-2 and VEGF expression in colon carcinoma cells by inhibiting the transcription factor AP-1[183]. In an *in vivo* study in which PGI_2 synthase was retrovirally transduced into C-26 colon adenocarcinoma cells and subsequently grafted to syngeneic BALB/c mice, the increased production of PGI_2 resulted in slower tumor growth and a decreased amount of vasculature[179].

When viewed in total, these findings suggest that relative levels of pro- and anti-angiogenic prostanoids in the tumor microenvironment might be strong determinants of the degree of angiogenesis that occurs in colorectal tumors.

LOX pathway in angiogenesis

A growing body of evidence indicates that LOX-catalyzed products (LTs and HETEs) also exhibit important biological effects on the angiogenic process in colon tumors. Ye *et al*[184] implicated 5-LOX in the promotion of colon cancer growth by nicotine through up-regulation of VEGF, MMP-2, and MMP-9, resulting in stimulation of angiogenesis in the colon. The same group also reported that cigarette smoke extract indirectly stimulated endothelial cell proliferation, a biological phenomenon that may enhance neo-angiogenesis[185,186]. CysLT1R antagonists were shown to impair angiogenesis in colon cancer xenografts[187], while LTB_4 was reported to induce neutrophil-mediated

vascular permeability[188]. Additionally, LTB_4 was shown to enhance hypoxia-induced microvascular alterations *in vivo*[189]. Expression of the LTB_4 receptor BLT2 was found to be highly inducible by VEGF, suggesting interplay among VEGF, BLT2, and BLT2 ligands during vascular angiogenesis[190]. Similarly, LTC_4 and LTD_4 also promoted angiogenesis *via* receptor-mediated interactions[191]. Moreover, reduced vascular permeability was observed in LTC_4 synthase knock-out mice which had impaired synthesis of cysteinyl LTs[192].

Very few reports have addressed the role of 15-LOX-1 in neo-angiogenesis in colorectal cancer. Recently, our group and others have shown that re-expression of 15-LOX-1 in colon cancer cell lines could reduce the expression and secretion of VEGF-A, and that treatment of HUVECs with conditioned medium from colon cancer cell lines ectopically expressing 15-LOX-1 resulted in reduced tube formation[159,193]. However, the signaling mechanism that medicates this angiostatic effect has not yet been reported.

Therefore, as with the prostanoids, it is likely that different bioactive lipids produced by the LOX pathway may have contrasting effects on angiogenesis, and their ultimate functional effects may be decided by the balance between 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 several different bioactive lipid mediators[194]. The timely resolution of inflammation prevents the development of chronic inflammation and fibrosis, and enables an organism regain a state of homeostasis[194].

The primary drivers of resolution include cessation of neutrophil infiltration and the nonphlogistic recruitment of macrophages to clear debris at the site of inflammation[194]. Lipoxins (Lx) were the first bioactive lipids to be identified as mediators of these processes. Lx's can be synthesized from AA in neutrophils through the enzymatic action of 5-LOX, and LTA_4 can be converted to LXA_4 and LXB_4 by 12-LOX in platelets upon the latter's adherence to neutrophils[195] (Figure 1). Additionally, AA can be metabolized by 15-LOX-1; after which, the oxygenated product can be converted to an epoxytetraene, and then to LXA_4 or LXB_4 by the action of hydrolases. ASA stimulates acetylation of COX-2, and thus shifts the activity of that enzyme from production of pro-inflammatory prostanoids to 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 lipoxin receptor/formyl peptide receptor (ALX/FPR2), which binds to LXA_4 and ATLs[18]. Although most 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].

LXA_4 expression or administration of LXA_4 analogs has been shown to reduce DSS-induced colitis[197]. Inflammatory stimuli in intestinal epithelial cells have been shown to initiate a feedback reaction which up-regulates expression of the LXA_4 receptor in intestinal epithelial cells[198]. Additionally, co-culture of Caco-2 cells with macrophages, where the cells were also treated with LXA_4, resulted in decreased secretion of pro-inflammatory cytokines[199], most likely due to inhibition of NF-κB. In a recent study which used colonic biopsies obtained from patients experiencing a remission of ulcerative colitis, significantly increased levels of LXA_4, along with enhanced expression of FPR2/ALX receptor mRNA and increased levels of macrophage infiltration were observed, suggesting that LXA_4 levels may play an important role in restoring mucosal homeostasis[200]. FPR2 expression was also shown to be increased in the colons of patients with Crohn's disease; again indicating that signaling through lipoxin was enhanced in the same inflammatory environments that were most likely to have enhanced 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), and formed by the concerted actions of acetylated COX-2, 5-LOX or 15-LOX[18] (Figure 1). Rvs have demonstrated potency at very low concentrations when administered orally or intravenously[18], and are known to signal through *ChemR23* and chemokine-like receptor 1 (CMKLR)[18]. RvD1 and RvD2 in the CACs of mice are known to be chemopreventive, and help reduce tumor growth[202]. RvE1 was reported to induce the clearance of neutrophils into the lumen of the gastrointestinal tract[203]. Moreover, RvE1 was shown to inhibit phosphorylation and activation of p65 NF-κB in the distal colons of mice in a DSS-colitis mouse model[199], suggesting its roles in both pro-resolution and anti-inflammatory pathways. Interestingly, the enzyme intestinal alkaline phosphatase (ALP1), a marker of differentiation, was shown to be induced in epithelial cells in the presence of RvE1, and also have a role in protecting against colitis[204]. Many of these potent bioactive molecules are currently being studied in 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 formation of LTB_4 and oxygenation of AA by 12-LOX, but enhance conversion of M1 inflammatory macrophages to the M2 phenotype[202]. Another recently identified intermediate is 13,14-dihydroxydocosahexaenoic acid (13,14-diHDHA or MaR2), which is synthesized when macrophages are co-incubated with 12-LOX and soluble epoxide hydrolase (sEH). This compound has been shown to reduce neutrophil migration and

enhance macrophage phagocytosis at nanogram concentrations[202]. MaR1 was recently used in a DSS and TNBS-induced mouse model of colitis. In that model, the disease activity index, amount of body weight loss, and tissue damage in the colon were all reduced. Additionally, there were significant decreases in the levels of inflammatory cytokines; most likely resulting from inhibition of the NF-κB pathway[206]. Moreover, in the same study, reduced migration of neutrophils, reduced ROS production, and reduced levels of inflammatory cytokines in LPS-stimulated bone marrow-derived macrophage cultures incubated with MaR1 were also reported[206].

CONCLUSION

There is no doubt that eicosanoids are an important family of immunoregulatory bioactive lipids with involvement in both the promotion and prevention of colon cancer. During inflammation, many of these autacoids act antagonistically or synergistically, and often in a temporal manner with the aid of different cell types in order to induce homeostasis. Many of these bioactive lipids are also essential for various cellular functions. Despite its importance, very few therapeutic agents 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 interferes with the COX pathway; however, ASA needs to be consumed long term (at least 5 years) to provide any protective effect against cancer. Furthermore, use of ASA is associated with significant bleeding events, and is therefore not suitable for all patients. COX-2 inhibitors that specifically target the inflammatory arm of the COX metabolic 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 originally designed for asthma have also not demonstrated high levels of efficacy[207]. Because inhibition of one pathway leads to activation of another due to the shunting of substrates, combined COX/LOX inhibitors have proved to be more effective than signal pathway inhibitors, and should be further studied in the context of CRC.

The scientific community needs to develop drugs that are specifically effective in cancer, and perhaps the most promising candidates include newly discovered resolution mediators such as lipoxins, resolvins, and mareisins. The results of early studies have indicated that these mediators are effective at very low concentrations, and therefore may be viable chemopreventive/therapeutic agents for use in CRC. It is also interesting to note that COX-2 and 5-LOX, that are associated with pro-carcinogenic events, and 15LOX-1, which is associated with anti-carcinogenic events in CRC, rarely show any mutations. Deregulation in their activity results from their overexpression, enhanced enzymatic activity or epigenetic silencing. Therefore, one may envisage the design and development of chromatin modifiers capable of reducing the expression of pro-inflammatory enzymes such as COX-2 and 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 highlighting the importance of eicosanoids in cancer. Delving into the details of how eicosanoids function in both tumor and stromal cells will be essential for understanding the pathways involved. Such knowledge will aid in the design of novel cancer therapies.

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