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Regulation of Inflammation in Cancer by Eicosanoids

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Abstract

Inflammation in the tumour microenvironment is now recognized as one of the hallmarks of cancer. Endogenously produced lipid autacoids, locally acting small molecule lipid mediators, play a central role in inflammation and tissue homeostasis, and have recently been implicated in cancer. A well-studied group of autacoid mediators that are the products of arachidonic acid metabolism include: the prostaglandins, leukotrienes, lipoxins and cytochrome P450 (CYP) derived bioactive products. These lipid mediators are collectively referred to as eicosanoids and are generated by distinct enzymatic systems initiated by cyclooxygenase (COX 1 and 2), lipoxygenases (5-LOX, 12-LOX, 15-LOXa, 15-LOXb), and cytochrome P450s, respectively. These pathways are the target of approved drugs for the treatment of inflammation, pain, asthma, allergies, and cardiovascular disorders. Beyond their potent anti-inflammatory and anti-cancer effects, non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 specific inhibitors have been evaluated in both preclinical tumor models and clinical trials. Eicosanoid biosynthesis and actions can also be directly influenced by nutrients in the diet, as evidenced by the emerging role of omega-3 fatty acids in cancer prevention and treatment. Most research dedicated to using eicosanoids to inhibit tumor-associated inflammation has focused on the COX and LOX pathways. Novel experimental approaches that demonstrate the anti-tumor effects of inhibiting cancer-

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associated inflammation currently include: eicosanoid receptor antagonism, overexpression of eicosanoid metabolizing enzymes, and the use of endogenous anti-inflammatory lipid mediators. Here we review the actions of eicosanoids on inflammation in the context of tumorigenesis. Eicosanoids may represent a missing link between inflammation and cancer and thus could serve as therapeutic target(s) for inhibiting tumor growth.

Keywords

Eicosanoids; Inflammation; Cancer; Metastasis; Tumor Microenvironment

1. Introduction

Inflammation is now recognized to be a critical component for tumor progression and one of the recently added “hallmarks of cancer” (1, 2). Inflammation is a biological response of vascularized tissues to noxious stimuli, such as chemical irritants or microbial pathogens. Epidemiological and genetic studies support the link between chronic inflammation and tumor progression (3). Inflammation and chronic infection are associated with tumorigenesis in one of every five cancer patients throughout the world (4). People with chronic inflammatory diseases are at increased risk of developing cancer of the respective inflamed tissue (5, 6) indicating that inflammation is, at least in part, cause and not an effect of cancer development. For example, chronic inflammation of the colon (ulcerative colitis) markedly increases the risk of developing colon cancer later in life (7, 8). Conversely, anti-inflammatory drugs decrease the risk of developing certain cancers. For instance, non-steroidal anti-inflammatory drugs (NSAIDs) reduce the risk of developing colon, breast, lung, and prostate cancer by reducing tumor associated-inflammation (9, 10). Selective anti-inflammatory COX-2 inhibitors can also decrease cancer incidence. While experimental evidence supports the causal relationship between inflammation and cancer, the molecular mechanisms and pathways linking inflammation and cancer remain not well understood. Eicosanoid generating enzymes, such as cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX), are over-expressed in several cancers including breast, lung, and pancreas (11). In addition, cancer patients have increased circulating markers of inflammation such as C-reactive protein (CRP), interleukin-6 (IL-6), and soluble tumour necrosis factor (TNF) receptors (12-14). Thus, novel biological therapies which target pro-inflammatory mediators including IL-6 and TNF- α are in clinical trials for cancer therapy (15).

Eicosanoids, including prostaglandins and leukotrienes, are products of local cell type specific arachidonic acid metabolism and can be potent mediators of inflammation (16-18). These lipid mediators play critical roles in diverse physiological and pathological processes, such as pulmonary fibrosis and cancer. The enzyme families cyclooxygenase (COX) and lipoxygenase (LOX) are responsible for the metabolism of arachidonic acid; this metabolism leads to the production of prostaglandins and leukotrienes, respectively. These enzymes are the target of approved drugs for the treatment of pain, inflammation, asthma, and allergies (18). Both of these pathways have been studied and implicated in cancer (11, 19). There is however, another prominent enzymatic pathway for which arachidonic acid is also the substrate, the cytochrome P450 (CYP) system. This eicosanoid pathway consists of two

main branches: ω -hydroxylases which converts arachidonic acid into hydroxyeicosatetraenoic acids (HETEs) and epoxygenases which converts it to epoxyeicosatrienoic acids (EETs). The CYP pathway is particularly relevant in tissues that express low COX and LOX activities. This CYP pathway, originally studied in conjunction with inflammatory and cardiovascular disease, appears to also have a role in tumor growth (20). While the COX and LOX-derived eicosanoids have already been intensely studied in tumor biology, investigation of cytochrome P450-derived eicosanoids has focused on their effects on inflammation and cardiovascular functions rather than cancer (16, 18, 20-23).

2. History of Inflammation and Cancer

Treating inflammation may have started around 400 BC with Hippocrates, a Greek physician, who used salicylates in willow tree bark to alleviate pain and fever, to symptoms associated with inflammation (24). In 1863 Rudolph Virchow was the first to notice leukocytes in neoplastic tissues and established the association between inflammation and cancer (3). In 1897 Felix Hoffman, a chemist with Friedrich Bayer & Co. in Germany, patented aspirin (acetyl-salicylic acid). In the late 1800s aspirin was introduced to the market to treat ailments such as arthritis. Much later, in 1971 Sir John Vane discovered the inhibition of prostaglandin biosynthesis as a mechanism of action for aspirin-like drugs (25). Vane was awarded the Nobel Prize for Medicine in 1982 with Bengt Samuelsson and Sune Bergstrom for their work on the identification of prostaglandins and the mechanism of aspirin (26, 27). In the 1990's two highly selective cyclooxygenase-2 (COX-2) inhibitors, the coxibs (celecoxib and rofecoxib) were developed to treat inflammation and pain. Many studies have now shown that these anti-inflammatory drugs (aspirin and COX-2 inhibitors) suppress tumor growth (11).

Over the past century, the anti-inflammatory mechanisms have focused on suppressing production of pro-inflammatory mediators, enzymes, or pathways. However, a new direction of inflammation research, spearheaded by the Serhan laboratory, has emerged with the discovery of novel autacoids such as lipoxins and resolvins as active, endogenous mediators of resolution (reviewed by Serhan) (28). Lipoxins, anti-inflammatory mediators which signal the resolution of inflammation, were first described by Serhan, Hamberg, and Samuelsson in 1984 (29). Resolvins, initially discovered by the Serhan laboratory, are novel anti-inflammatory and pro-resolving endogenous lipid mediators derived from the omega-3 fatty acids eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA). These potent mediators are biosynthesized by LOX, cytochrome P450, and COX-2 dependent routes. Resolvins can be produced in the presence or absence of aspirin and in the presence of statins (30, 31).

3. Overview of biochemistry and pharmacology of eicosanoids

Eicosanoids consist of several relatively large families derived from polyunsaturated fatty acids, (omega-6 fatty acids or omega-3 fatty acids). The term eicosanoid is derived from the Greek "eicosa" for twenty and is the collective term for oxygenated 20-carbon essential fatty acids. The subscript of a particular eicosanoid represents the number of double bonds; for example arachidonic acid (AA)-derived prostaglandins have two double bonds (e.g. PGE₂).

Eicosanoids are generated via the oxidation of 20-carbon chain fatty acids (18). The omega-6 family of eicosanoids encompasses the well characterized prostanoids and leukotrienes generated from cyclooxygenases and lipoxygenases (16) (Figure 1A). The omega-3 family of eicosanoids includes: EPA- and DHA-derived resolvins and protectins (32) (Figure 1B). In addition, the omega-3 derived inflammatory exudates mediators appear to be biosynthesized in inflammatory exudates via their direct flow from peripheral blood into evolving exudates (33). Eicosanoids act locally and have a relatively short half-life, ranging from seconds to minutes (34). The mode of action for eicosanoids includes binding to a specific G protein-coupled receptor which has allowed for the development of specific receptor agonists and antagonists (34). Eicosanoids may initiate both the inflammatory response as well as mediate resolution of inflammation (28, 35). The biochemistry and biosynthesis of these diverse types of eicosanoids are out of the scope of this review and we refer to the recent reviews by Serhan (17), Zeldin (16) and others (11). Here we focus on the biological effects of several eicosanoid pathways, studied to date, related to inflammation and cancer.

3. Inflammation in cancer

Epidemiological data supports that about 20% of cancer deaths are linked to unabated inflammation and chronic infections (3, 36). Examples include inflammatory bowel diseases, leading to colorectal cancer; bronchitis, leading to lung cancer; and prostatitis, leading to prostate cancer (as reviewed by Agarwal) (36). Most precancerous and cancerous tissue have signs of inflammation including innate immune cells, cytokines, and chemokines (37). Many studies support that cancer-associated inflammation stimulates tumor progression (as reviewed by Mantovani) (37). Colon carcinoma and cervical carcinoma are among the best examples of inflammation-associated cancer (37). Coussens *et al* described, in a seminal publication, a genetically engineered mouse model demonstrating inflammation is critical for carcinogenesis (38). We have previously demonstrated that anti-inflammatory drugs such as PPAR ligands and COX-2 inhibitors can inhibit tumor growth by suppressing inflammation and angiogenesis (39-43).

In 1971 Folkman shifted the focus of cancer research from tumor cells toward stromal cells such as endothelial cells (44). Since then, the contributions of non-cancerous cells to the growth of tumors has extended to non-local cells, including bone-marrow derived macrophages, neutrophils, mast cells, and mesenchymal stem cells, contributing to the invasiveness and metastatic ability of neoplastic epithelial cells (45, 46).

Macrophages in inflammatory diseases, for example in inflammatory bowel disease, are phenotypically different from normal macrophages in that they can secrete many cytokines such as IL-1, IL-6, and TNF- α (47). These pro-inflammatory cytokines can promote metastasis (48) and contribute to tumor growth by inducing chemokines (49). Pro-inflammatory cytokines induce adhesion molecules and metalloproteinases, resulting in tumor invasion and metastasis (50). Pro-inflammatory mediators, including IL-6, TNF- α , and versican, act as macrophage activators to enhance metastatic growth and angiogenesis (51). Based on these and other studies, cancer-related inflammation has been reported to be one of the newest hallmarks of cancer (1). The following cell types can modulate tumor

growth, metastasis, and tumor angiogenesis: tumor associated macrophages, neutrophils, myeloid-derived suppressor cells and dendritic cells (3, 52). Inflammation has been shown to have both pro- and anti-tumorigenic activity. Blocking inflammation has been associated with the stimulation of cancer while inflammatory infiltration of lymphocytic/monocytic cells has been shown to inhibit tumor growth (11, 53-55). Therefore, inflammation in the tumor bed can either stimulate or inhibit tumor growth (41, 54, 56). Thus, pharmacological modulation of inflammation in cancer treatments must be evaluated with the notion that inflammation may be a double-edged sword in this field.

It has been recognized that tumor growth is a complex process involving many cell types. The intercellular communication that takes place between these cells is conducted by an array of soluble factors such as: proteinaceous growth factors and chemokines, VEGF, FGF₂, TGF- β , TNF- α , IL-1, and oxygen radicals (57). Minimal attention has been paid to small molecule mediators (i.e. lipid autacoids) whose role in cancer has only recently emerged (58). Levels of eicosanoids increase progressively in patients with benign pelvic disease compared to those with epithelial ovarian cancer (58). In another example, endogenous levels of arachidonic acid and certain eicosanoids are elevated in human colorectal cancer in comparison to normal colon mucosae (59).

4. Cyclooxygenase-derived eicosanoids in cancer

Most research on eicosanoids in inflammation and cancer has focused on the COX pathways. The COX pathways produce five major prostanoids (prostaglandin D₂, prostaglandin E₂, prostaglandin F_{2 α} , prostaglandin I₂ and thromboxane A₂) which have important roles in tissue homeostasis (60, 61). COX-2 is a critical enzyme in the regulation of inflammation and plays an important role in cancer-associated inflammation, tumor progression, and metastasis (61, 62). The DuBois laboratory was the first to report that COX-2 is up-regulated in human colorectal adenomas and adenocarcinomas (63) and identified a key role for COX-2 in inflammatory bowel disease and colorectal cancer (64). Therefore, COX-2 has been targeted in many cancers including: colon cancer, colorectal cancer, breast cancer, gliomas, prostate cancer, esophageal carcinoma, pancreatic cancer, lung carcinoma, gastric carcinoma, ovarian cancer, Kaposi's sarcoma and melanoma (36, 65). Cancer patients with tumors having increased COX-2 expression exhibit decreased survival rates (11). The role of COX-2 and PGE₂ in inflammation and cancer has been extensively reviewed (12, 36, 62, 64).

COX-2 derived prostaglandins are important in the early phases of the inflammatory response and the resolution of inflammation (66, 67). Aspirin and other NSAIDs inhibit COX enzymes which decrease prostaglandin levels resulting in anti-inflammatory and anti-tumor activity (11). Targeting downstream prostanoids has provided a strategy to inhibit tumor progression (61). The decreased incidence of esophageal, colorectal, bladder, lung, and gastric cancer treated with aspirin and other NSAIDs demonstrates the importance of COX-2 in many cancers (36). While NSAIDs have potent anti-cancer activity clinically, their cardiovascular and gastrointestinal side effects have curtailed their long term use (11, 60).

While elevated levels of pro-carcinogenic prostaglandins are found in several human malignancies, PGE₂ is the most common prostaglandin found in different human cancers including colon, lung, breast, and head and neck cancers. The up-regulation of PGE₂ is associated with a poor prognosis (11, 68-71). In patients with head and neck cancers there was an inverse correlation between PGE₂ levels and tumor stage (71). Serum levels of PGE₂ were significantly decreased after successful treatment. Many studies on enzymes and receptors demonstrate that cyclooxygenase-2 (COX)-derived PGE₂ promotes colon carcinoma invasion and growth in several mouse models of cancer (72-74). Consistent with the pro-tumorigenic role of PGE₂, mice deficient in PGE₂ production exhibit decreased tumorigenesis. Genetic deletion of microsomal PGE₂ synthase 1 (mPGES-1), which generates PGE₂, results in suppression of intestinal cancer growth by 66-95% (75). Mice genetically deficient in phospholipase A₂ (PLA₂), an enzyme that releases arachidonic acid from the cell membrane, exhibit decreased lung tumorigenesis that may be mediated by decreased prostaglandin synthesis (76).

Another crucial mechanism for the potent pro-tumorigenic activity of PGE₂ is the local suppression of the immune responses (49). PGE₂ inhibits macrophage, T cell, and natural killer cell activation, resulting in immunosuppressive and pro-tumorigenic activity (77, 78). Increased pro-inflammatory cytokines are required for tumor invasion, angiogenesis, and tumor growth (79, 80). The pro-inflammatory cytokine IL-1 β induces the formation of myeloid-derived suppressor cells (MDSC), which are expressed in various cancers and suppress anti-tumor immune responses thereby allowing the proliferation of cancer cells (81). PGE₂ promotes tumor progression by inducing MDSC; this provides a therapeutic approach for anti-cancer therapy (82).

In addition to blocking prostaglandin production, another strategy to inhibit experimental tumor growth is overexpression of eicosanoid metabolizing enzymes, such as 15-hydroxyprostaglandin dehydrogenase (15-PGDH), which is responsible for the enzymatic degradation of PGE₂. 15-PGDH activity is down-regulated in human colorectal carcinomas, breast cancer, non-small cell lung cancer, gastric cancer, and bladder cancer, suggesting a tumor suppressive role of 15-PGDH (83-88).

The discovery of eicosanoid receptors has allowed for the inhibition of cancer-associated inflammation and tumor growth by inhibiting their activity (11, 61, 89). Mice deficient of PGE₂ receptors (EP₁, EP₂ or EP₄) exhibit decreased tumorigenesis (60, 90, 91). Conversely, knockout mice of PGE₂ receptor exhibit increased tumorigenesis, suggesting a protective role in cancer (92). In addition to genetic disruption of PGE₂ receptors, administration of PGE₂ receptor antagonists may inhibit tumor growth or even act as chemo-preventative agents (90, 93, 94). While PGE₂ stimulates cancer migration, the PGE₂ EP₁ and EP₄ receptor antagonists inhibited tumor cell migration and tumor metastasis (95, 96). Administration of soluble EP₂ has been shown to inhibit osteolytic tumor growth by neutralizing PGE₂ cell signaling (97). Anti-EP therapy and anti-COX-2 may have therapeutic efficacy in Kaposi's Sarcoma by further reducing chronic inflammation (98).

In contrast to PGE₂, prostaglandin D₂ (PGD₂) exhibits both pro- and anti-tumorigenic activity in various experimental models (11, 78). PGD₂ exhibits anti-cancer effects as

hematopoietic prostaglandin D synthase, which synthesizes PGD₂, suppresses intestinal adenomas by 80%. Disruption of the gene for hematopoietic PGD synthase leads to 50% more intestinal adenomas as compared to controls (99). Hematopoietic PGD synthase was detected mainly in macrophages and monocytes of the gut mucosa (99). In contrast treatment of a colitis model in rats with a selective PGD₂ receptor (DP1) antagonist suggest that prolonged elevation of PGD₂ synthesis after resolution of colitis may contribute to colitis-associated colorectal cancer (100). Prostaglandin D₂ and its receptor (DP1) were recently demonstrated to be up-regulated in individuals in long-term remission from ulcerative colitis (101). In contrast patients with active ulcerative colitis demonstrated increased expression of several pro-inflammatory cytokines and PGE₂ synthesis (101).

We and others have demonstrated the anti-tumor activity of COX-2 inhibitors in inflammation-associated experimental tumor models including transplantable and genetically engineered models of cancer (36, 43, 102-104). COX-2 inhibitors initially did not exhibit the toxicity associated with aspirin, such as gastrointestinal bleeding. Over a decade ago, celecoxib was shown to significantly reduce adenoma size and number with no toxicity in patients with familial adenomatous polyposis (FAP) (105). Subsequently three major clinical trials demonstrated significant inhibition of adenoma growth in patients at high risk for colorectal carcinoma, all three trials were terminated because of cardiovascular toxicity and death as well as gastrointestinal complications (106-108). COX-2 inhibitors increase cardiovascular risk and are not recommended for patients, especially those with a history of atherosclerotic disease (11, 109, 110). Celecoxib remains approved by the FDA for the treatment of colon and rectal polyps in patients with familial adenomatous polyposis (11). However, the toxicities of COX-2 inhibitors underscore the importance of developing novel classes of anti-inflammatory agents for cancer therapy.

Aspirin has emerged as the best candidate for use in chemoprevention because of its known cardiovascular benefit, safety, and efficacy data (110, 111). Aspirin promotes the formation of antiproliferative aspirin-triggered lipoxins (ATLs, or 15-epi-lipoxin) (112). ATLs were generated by a human lung adenocarcinoma cell line (A549)-neutrophil interactions (17). These endogenous anti-inflammatory aspirin-triggered lipoxins may mediate part of the anti-inflammatory and anti-cancer activity of aspirin (112).

5. Lipoxygenase-derived eicosanoids and cancer

While the cyclooxygenase pathways have been the most extensively studied pathways in eicosanoids related to cancer, the lipoxygenase (LOX) pathways also have an important role in tumor progression and survival (113). The principal lipoxygenases expressed in humans are 5-lipoxygenase (5-LOX), 12-lipoxygenase (12-LOX), and 15-lipoxygenase (15-LOX; that exists in at least 2 main forms Type 1 and 2). 5-LOX and 12-LOX stimulate angiogenesis and tumor growth (114-116), 15-LOX-2 has an anti-tumorigenic role while 15-LOX-1 can have both pro-tumorigenic and anti-tumorigenic activity (113). Both leukotrienes and lipoxins have an emerging role in cancer. Indeed, lipoxygenases were recently demonstrated to mediate invasion of intrametastatic lymphatic vessels and lymph node metastasis in ductal mammary carcinoma (117).

The 5-lipoxygenase (5-LOX) pathway is implicated in the development and progression of human cancers. 5-LOX, whose crystal structure was recently identified (118), is a key enzyme in metabolizing arachidonic acid to leukotrienes. 5-LOX can be induced by pro-inflammatory stimuli and is expressed in epithelial cancers including lung, prostate, breast, and colon (113). Hence, 5-LOX inhibitors have been targeted for their chemopreventive effects. Inhibition of 5-LOX activity is shown to block prostate cancer cell proliferation as well as carcinogen-induced lung tumorigenesis (119, 120).

Inflammation-associated cancers express both 5-LOX and COX-2 proteins (121). The combination of a 5-LOX inhibitor and a COX-2 inhibitor is more potent in several tumor models (lung, colon, skin, pancreas, and esophageal cancer) than inhibiting either eicosanoid pathway alone (114, 119, 122-124). This inhibition of tumor growth was accompanied by the downregulation of PGE₂ and LTB₄ (122). Dual COX/5-LOX inhibitors are being developed and can induce tumor cell apoptosis independent of the arachidonic acid pathway (125, 126).

12-lipoxygenase (LOX), the main human 12-HETE generating enzyme, has also been shown to be involved in both cancer cell proliferation and survival. Inhibition of 12-LOX blocks cell proliferation and induces apoptosis in carcinoma cells. Guo *et al* recently demonstrated that 12-lipoxygenase is involved in the regulation of ovarian cancer cell growth and survival and is a therapeutic target for ovarian cancer patients (127). These studies show that 12-LOX expression is higher in high-grade serous ovarian carcinoma compared to normal epithelium and inhibition of 12-LOX by siRNA reduced tumor cell growth (127). Another lipoxygenase that contributes to inflammation and subsequent cancer development is 15-lipoxygenase-1 (15-LOX-1). 15-LOX-1 is expressed in cancers such as Hodgkin lymphoma and colorectal cancer and 15-LOX-1 derived metabolites contribute to the tumor-associated inflammation of Hodgkin lymphoma (128, 129).

The lipoxygenase (LOX) pathways convert arachidonic acid to leukotrienes. In contrast to prostaglandins, which act quickly and degraded more rapidly, leukotrienes have a half-life around 4 hours (12). Inflammatory cells including leukocytes, macrophages, and mast cells can synthesize leukotrienes such as leukotriene A₄ (LTA₄) and leukotriene B₄ (LTB₄) (130). The levels of LTB₄, the main product of the 5-LOX pathway, were higher in prostate cancer samples than pericancerous samples (131). LTB₄ can promote the growth of inflammation-induced melanoma (132). Furthermore, a LTB₄ receptor antagonist suppressed inflammation-associated tumor growth (132). The LTB₄ receptor antagonist, LY293111, inhibited colon cancer tumor growth and induced apoptosis *in vitro* (133). The combination of the LTB₄ receptor antagonist, LY293111, and gemcitabine was most effective on tumor growth and metastases in an orthotopic model of pancreatic cancer (134). However, this combination did not improve progression-free survival in Phase II clinical trial of pancreatic cancer or non-small-cell lung cancer (135). Another pro-inflammatory mediator derived from 5-LOX metabolism of the arachidonic acid cascade is leukotriene D₄ (LTD₄). LTD₄ is overexpressed in several cancers and levels of circulating LTD₄ are elevated in patients with hepatocellular carcinoma and chronic hepatitis B (136).

Both 5-HETE and 12-HETE are also products of lipoxygenase and are involved in tumor progression (12). Exogenous 5-HETE can stimulate the proliferation of prostate cancer cells and act as a survival factor (137, 138). These results require relatively high concentrations (at a concentration of 10 μ M). Blocking the formation of 5-HETE, by inhibiting 5-lipoxygenase, results in massive apoptosis of human prostate cancer cells (139). 12-HETE also has a critical role in tumor metastasis, including tumor cell motility, tumor cell-vasculature interactions, invasion, and angiogenesis (140). 12-lipoxygenase is widely expressed in tumor cell lines, providing a target for cancer therapy (141). In recent studies, Kerjaschki et al demonstrates the presence of metastatic tumor cells in sentinel lymph nodes of human mammary carcinomas that express 15-lipoxygenase-1 (ALOX15) and 12S-HETE. By inhibiting 15-lipoxygenase-1, lymph node metastasis was suppressed (117). While 5-HETE, 12-HETE, and 20-HETE have mitogenic and pro-tumorigenic activity, HETEs such as 8-HETE and 11-HETE are reported to have anti-mitogenic and anti-tumor activity (142). An antitumorigenic, prodifferentiating, and tumor suppressing role has been identified for 8S-LOX, and its metabolite 8-HETE, in skin carcinogenesis (143). 8-HETE induces growth inhibition in premalignant epithelial cells (144). Levels of 5-HETE and 12-HETE increase progressively in patients with pelvic disease to those with epithelial ovarian cancer while 15-HETE may disrupt cancer progression (58).

Conversely, lipoxins, which are also lipoxygenase-derived eicosanoids, are formed during the resolution of inflammation and are considered to be anti-tumorigenic (29). Lipoxin A₄ (LXA₄) and lipoxin B₄ (LXB₄) are the two principal lipoxins generated and have been shown to be potent mediators of the resolution of inflammation. Lipoxins have potent endogenous activity in stimulating monocytes non-phlogistically, i.e. not causing the release of pro-inflammatory mediators or reactive oxygen species (28). Lipoxins stimulate macrophages to phagocytose apoptotic neutrophils (145). Macrophages also appear to be important as they clear up apoptotic neutrophils and cellular debris as part of the resolution of inflammation (28). For more biochemical details please refer to Serhan et al (17). Of interest, inhibitors of the LTA₄ hydrolase or soluble epoxide hydrolase lead to an increase in endogenous lipoxin levels (146, 147) that regulate inflammation and could be a useful strategy for certain cancer treatments.

A novel approach to cancer therapy is the administration of endogenous anti-inflammatory lipid mediators such as lipoxins. Lipoxin A₄ (LXA₄) reduces cell proliferation, inhibits tumor cell invasion, and suppresses experimental tumor growth (112, 148-150). LXA₄ exhibits anti-inflammatory actions in human astrocytoma cells by inhibiting pro-inflammatory chemokine IL-8 and the adhesion molecule ICAM-1 (151).

6. Cytochrome P450-derived eicosanoids and cancer

Cytochrome P450 (CYP)-dependent metabolism of arachidonic acid occurs in several tissues including liver, kidney, and the cardiovascular system. The CYP enzymes relevant to arachidonic acid metabolism include two distinct pathways: the ω -hydroxylases and epoxygenases. The ω -hydroxylases of the 4A and 4F gene families of cytochrome P450 (CYP4A and CYP4F) convert arachidonic acid to autacoids such as hydroxyeicosatetraenoic acids (HETEs). The epoxygenase pathway is encoded predominantly by the CYP2C and

CYP2J genes and generates epoxyeicosatrienoic acids (EETs), which have demonstrated anti-inflammatory activity (16, 152, 153). EETs are then further metabolized mainly by soluble epoxide hydrolase (sEH) to the dihydroxyeicosatrienoic acids (DHETs), which have traditionally been considered to be less active than EETs (154, 155).

The role of LOX-derived and CYP-derived HETEs in cancer biology has been extensively reviewed by Moreno (142). In 2008, U251 glioblastoma cells were genetically altered (transfected with rat CYP4A1 cDNA) to increase the formation of 20-HETE (156). This stimulated tumor cell proliferation in culture. When these U251 glioblastoma cells were implanted into the brain of rats, a 10-fold increase in tumor volume versus animals receiving mock-transfected U251 cells was observed (156). In contrast to the strategy to increase 20-HETE, Guo *et al* demonstrated that HET0016 significantly inhibited human U251 glioblastoma cell proliferation in a dose-dependent manner (157). Subsequently, the same group demonstrated that 9L gliosarcoma proliferation and tumor growth in rats were suppressed by HET0016 (158). Systemic administration of HET0016 inhibited the tumor growth of 9L gliosarcomas by 80%, and tumor angiogenesis by roughly 50%. In a separate study, HET0016 and a 20-HETE antagonist (WIT002) both inhibited the proliferation of a renal adenocarcinoma. This cell type expressed CYP4F isoforms and produced 20-HETE (159). Recent studies show that CYP ω -hydroxylase (via CYP4A11 transfection of tumor cells) promoted angiogenesis and metastasis associated with an increase of VEGF and MMP9 in non-small cell lung cancer cells (160). Little is known about 20-HETE in cancer patients. In one study, 12-HETE and 20-HETE concentrations were shown to be elevated in the urine of patients with benign prostatic hypertrophy and prostate cancer patients as compared to normal subjects (161). Further analysis did not establish a correlation between the concentrations of HETEs and prostatic specific antigen (PSA) level, gland size, or tumor grade (161).

Pioneering studies from the Hammock laboratory demonstrate that soluble epoxide hydrolase is a therapeutic target for inflammation (18, 147). In contrast to COX/LOX inhibitors, which directly inhibit the production of pro-inflammatory mediators, soluble epoxide hydrolase inhibitors promote the formation of pro-resolution mediators such as lipoxin A₄ (147). Soluble epoxide hydrolase inhibitors, such as 12-(3-adamantan-1-yl-ureido)-dodecanoic acid butyl ester (AUDA-BE), stabilize anti-inflammatory EETs, which indirectly reduce the expression of COX-2, 5-LOX, iNOS, and VCAM-1 (162, 163). AUDA-BE decreased protein expression of COX-2 without altering COX-1 expression and decreased inflammatory eicosanoids such as PGE₂ levels in lipopolysaccharide (LPS)-challenged mice (162). When AUDA-BE was used in combination with low doses of indomethacin, celecoxib, or rofecoxib, PGE₂ concentrations were reduced with no effects on prostacyclin and thromboxane levels. Thus, soluble epoxide hydrolase inhibitors synergize with NSAIDs and COX-2 inhibitors in suppressing inflammation (162).

Administration of a soluble epoxide hydrolase inhibitor in a mouse colitis model resulted in decreased ulcer incidence (163). Based on the anti-inflammatory effects of soluble epoxide hydrolase inhibitors, one may expect these agents to have anti-cancer effects based solely on their anti-inflammatory activity. However, soluble epoxide hydrolase inhibitors exhibit pro-

angiogenic activity (164) since tumor growth is angiogenesis-dependent (165), soluble epoxide hydrolase inhibitors may have a bi-phasic effect on tumor growth.

The expression of sEH, the main metabolizing enzyme of EETs, has been investigated in cancer. The loss of sEH, has been reported in hepatocellular carcinoma and hepatoma cells (166, 167). Enayetallah *et al* further confirmed that sEH is down-regulated in renal and hepatic tumors, in principle increasing the levels of EETs in the tumor tissue (168). These studies support a potential role for EETs in cancer due to its metabolizing enzyme being down-regulated. However, the expression of sEH has been shown to be up-regulated in seminoma, cholangiocarcinoma, and advanced ovarian cancer when compared to normal tissues or early stage cancer (168). In preliminary studies on human tissues, sEH expression was increased in ulcerative colitis, ulcerative-induced dysplasia, and ulcerative colitis-induced carcinoma (163). Thus, there is no consistent finding in the expression of sEH in tumors. If EETs promotes tumor growth, sEH would be expected to be down-regulated in tumors – which is observed only in certain tumors.

7. Omega-3 fatty acids and cancer

Eicosanoid biosynthesis and actions can be directly influenced by nutrients in the diet, as evidenced by the emerging role of omega-3 fatty acids in cancer prevention and treatment. Dietary fat may contribute to cancer-associated inflammation through abnormal arachidonic acid metabolism (11). A Western-style diet can increase risk of tumorigenesis via macrophage recruitment and subsequent activation of TNF- α , PGE₂, NF- κ B and Wnt inflammatory pathways (169). Arachidonic acid can make up to 40% of the fatty acid composition of cancer cell membranes (12). The anti-tumorigenic effects of omega-3 polyunsaturated fatty acids (PUFAs) may be partly mediated by their anti-inflammatory effects (170). Omega-3 PUFAs inhibit carcinogenesis associated with a reduction in pro-inflammatory cytokines (171). FAT-1 transgenic mice, which have increased endogenous omega-3 PUFAs, exhibit decreased tumorigenesis associated with reduced pro-inflammatory factors such as TNF- α (172). The role of omega-3 fatty acids in cancer has been recently reviewed (173, 174)

Resolvins of the E series are novel endogenous anti-inflammatory and pro-resolving lipid mediators derived from the omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) (175). The E-series resolvins include Resolvin E1 (RvE1) and Resolvin E2 (RvE2) (176). Serhan *et al* first identified resolvins from murine resolving exudates *in vivo* (30). These resolvins display potent efficacy in treating diseases driven by inflammation. When aspirin is added to EPA, aspirin irreversibly acetylates the COX enzyme, generating COX-2 dependent RvE1 (177). Cytochrome P450 metabolism of EPA can also generate the precursors of resolvins of the E series (178).

Resolvins of the D series are a novel family of endogenous lipid autacoids that are derived from the omega-3 fatty acid docosahexaenoic acid (DHA) by the sequential actions enzymes 5-LOX and 15-LOX or by an acetylated COX-2 (179). Docosahexaenoic acid (DHA) is an omega-3 fatty acid which result in decreased formation of arachidonic acid-derived PGE₂ (180). Omega-3 PUFA counter-regulate arachidonic acid-derived eicosanoids in humans,

animals, and cells (180). Resolvins have been shown to play a pivotal role in the resolution of inflammation (179). For example, the combination of DHA and a COX-2 inhibitor, two anti-inflammatory agents, resulted in synergistic cytotoxicity in neuroblastoma cells (173). Similarly, the combination of DHA and COX-2 inhibitors inhibited prostate cancer and melanoma cell growth (181, 182).

A new direction of inflammation research, spearheaded by the Serhan laboratory, has emerged with the stimulation of resolution and the discovery of endogenous non-phlogistic chemical mediators of resolution (28). Endogenous anti-inflammatory mechanisms may have a role in carcinogenesis (15, 78). In contrast to normal neural cells, neuroblastoma tumor cells do not generate the anti-inflammatory and endogenous lipid mediators, resolvins and protectins (183). The potential role of resolvins and protectins in cancer remains of interest.

8. Outlook

Many classes of drugs which were originally found to modulate inflammation and cardiovascular diseases have been shown to also have substantial effects on cancer growth. This appears to also be the case with eicosanoids, such as prostaglandins. Other eicosanoid mediators of inflammation, including leukotrienes, lipoxins, and HETEs, have received new attention as targets in cancer therapy. Therefore, additional eicosanoid pathways should also be evaluated for their potential impact in specific cancers as new therapeutic approaches. Future studies will be needed to determine if targeting products of the arachidonic acid cascade (using eicosanoid receptor antagonists or manipulating their metabolizing enzymes) or modulating endogenous lipid mediators (leukotrienes or lipoxins) directly can be used to control tumor-associated inflammation in cancer patients. Multiple inflammatory pathways should be targeted; a strategy now commonly used for cancer therapy in order to conquer the inherent resilience of tumor cells to selective single-target therapies. The design of such multi-prong approaches will be facilitated by our rapidly increasing knowledge of the many pathways that underlie the regulation of eicosanoid production in inflammation. On the other hand, we are still in the beginning of unraveling the multifaceted biological activities of eicosanoids in tumor-associated inflammatory processes. Sorting out the various modes of action of eicosanoids and their cellular targets in the tumor microenvironment is crucial to understanding the complex local actions of these lipid mediators in cancer. This will be paramount if the potent biological activities of eicosanoids are to be harnessed for the development of novel cancer therapies.

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Abbreviations

AA	arachidonic acid
CYP and P450	cytochrome P450

COX	cyclooxygenase
LOX	lipoxygenase
NSAID	non-steroidal anti-inflammatory drug
CRP	C-reactive protein
IL-6	interleukin-6
TNF	tumour necrosis factor
EET	epoxyeicosatrienoic acid
HETE	hydroxyeicosatetraenoic acid
(EPA)	eicosapentaenoic acid
(DHA)	docosahexaenoic acid
LXA₄	lipoxin A ₄
LTB₄	leukotriene B ₄
NF-κB	nuclear factor-kappaB
sEH	soluble epoxide hydrolase
DHET	dihydroxyeicosatrienoic acid
PGE₂	prostaglandin E ₂
PGI₂	prostacyclin
VEGF	vascular endothelial growth factor
VEGF;FGF-2	fibroblast growth factor-2
TGF-β	transforming growth factor-beta
mPGES-1	microsomal PGE ₂ synthase 1
PLA₂	phospholipase A ₂
MDSC	myeloid-derived suppressor cells
15-PDGH	15-hydroxyprostaglandin dehydrogenase
EP2 receptor	prostaglandin E ₂ receptor
IFNγ	interferon-gamma
FDA	Food and Drug Administration
ATL	aspirin-triggered lipoxin
15-epi-LXA₄	aspirin-triggered lipoxin A ₄
ICAM	intracellular adhesion molecule
iNOS	inducible nitric oxide synthase
VCAM-1	vascular cell adhesion molecule-1

AUDA-BE	12-(3-adamantan-1-yl-ureido)-dodecanoic acid butyl ester
LPS	lipopolysaccharide
RvE1	Resolvin E1
PUFA	polyunsaturated fatty acid

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Highlights

1. Inflammation in the tumor stroma is now recognized as a hallmark of cancer.
2. Eicosanoids may inhibit cancer growth by reducing tumor-associated inflammation.
3. Eicosanoids may represent a missing link between inflammation and cancer.
4. Drugs targeting eicosanoid pathways exhibit potent anti-inflammatory effects.
5. Most research on eicosanoids in cancer has focused on the COX and LOX pathways.

Figure 1A. Bioactive eicosanoids derived from the omega-6 family

Arachidonic acid is metabolized by distinct enzymatic systems initiated by cyclooxygenase (COX 1 and 2), lipoxygenases (5-LOX and 15-LOX), and cytochrome (CYP) P450s. Schematic overview of major mediators and their metabolites (blue); enzymes (black, boxed), biological role (green). Inhibitors (red ovals). HETE, Hydroxyeicosatetraenoic acids; EETs, epoxyeicosatrienoic acids; CYP, cytochrome P450 enzymes. The sEH inhibitor (soluble epoxide hydrolase inhibitors) increase EET levels hence act as agonist of the EET pathway. PGE₂, prostaglandin E₂; PGI₂, prostacyclin; LXA₄, lipoxin A₄; LTA₄, leukotriene A₄; 15-epi-LXA₄, aspirin-triggered lipoxin A₄; DHET, dihydroxyeicosatrienoic acid; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase.

Figure 1B. Bioactive eicosanoids derived from the omega-3 family

The omega-3 family of eicosanoids includes: eicosapentaenoic acid (EPA)- and docosahexaenoic acid (DHA)-derived resolvins and protectins. EPA and DHA are metabolized by distinct enzymatic systems initiated by cyclooxygenase (COX-2) and lipoxygenases (5-LOX and 15-LOX). Schematic overview of major mediators and their metabolites (blue); enzymes (black, boxed), biological role (green).