[Frontiers in Bioscience 12, 1574-1585, January 1, 2007]

Cyclooxygenases and lipoxygenases in prostate and breast cancers

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TABLE OF CONTENTS

1. ABSTRACT

Oxidative metabolism of polyunsaturated fatty acids through cyclooxygenases or lipoxygenases can generate various lipid peroxides and bioactive lipids, and regulate cellular proliferation, apoptosis, differentiation and senescence. The role of the second cyclooxygenase isoform (COX-2) has been demonstrated in a number of studies and is regarded as a promising target for chemoprevention and treatment. The involvement for lipoxygenases in tumor initiation and progression has been implicated in several studies but remains controversial. Among the many members of lipoxygenase family, both tumor promoting and suppressing activities have been described. For example, 15-lipoxygenase-1 has been implicated as a tumor promoter in prostate cancer, but it suppresses colon cancer. In this review, the role of cyclooxygenases and lipoxygenases in cancer will be described, with the hope of attracting further research to define their functions in cancer.

2. OXIDATIVE METABOLISM OF LIPIDS

Excessive consumption of fat is a risk factor for cancer (1). Polyunsaturated fatty acids (PUFA), such as arachidonic acid and its precursor, linoleic acid, are major ingredients in animal fats and also in many vegetable oils. Arachidonic acid can be oxidized by cyclooxygenases (COX), lipoxygenases (LO or LOX), or P450 epoxygenase to form a variety of bioactive lipids, including prostaglandins (2) . Other PUFAs such as linoleic acid can also be oxidized by some members in the LOX or P450 monoxygenase family to form biologically active lipids.

The oxidative metabolism of arachidonic acid through the COX pathway generates five primary prostanoids: prostaglandin(PG) D_2, prostaglandin E_2, prostaglandin $F_{2\alpha}$, prostaglandin I_2 (PGI_2), and thromboxane A_2 (TxA_2). The biosynthesis of prostanoids involves a three-step sequence of stimulus-initiated release of arachidonic acid from phospholipids involving secretory,

cytoplasmic or both types of phospholipase A_2 ($sPLA_2$, $cPLA_2$) (3); oxygenation of arachidonic acid, yielding prostaglandin H_2 (PGH_2) by COX (also know as prostaglandin H_2 synthases, PGHS); and subsequent conversion of PGH_2 to five primary prostanoids PGD_2, PGE_2, PGF_2, PGI_2, or TxA_2 via specific synthases (or isomerases) (4-9). Prostanoids possess potent biological activities and regulate immune function, kidney development, reproductive biology, and gastrointestinal integrity. They also modulate platelet aggregation, renal homeostasis, vascular homeostasis, uterine function, embryo implantation and labor, sleep wake cycle, body temperature, gastric mucosa protection, and inflammation (10).

Lipoxygenases consists of a family of non-heme iron containing proteins that catalyze the dioxygenation of PUFAs containing the 1-*cis*-4-*cis*-pentadiene moiety, including arachidonic acid, to form bioactive lipids. Metabolism of arachidonic acid by lipoxygenases generates regioisomeric cis/trans conjugated hydroxyeicosatetraenoic acids (HETEs), leukotrienes, lipoxins, and hepoxilins. Dependent on the predominant position of the incorporation of hydroperoxy function, lipoxygenases are classfied as 5-, 8-, 12-, and 15-lipoxygenases (LO or LOXs), whose main products are 5(S)-, 8(S)-, 12(S), and 15(S)-HETE, respectively. Lipoxygenase metabolites, including hydroperoxy and hydroxyl fatty acids, have been implicated in cell proliferation, differentiation, and apoptosis.

In the P450 monoxygenase pathway, arachidonic acid is converted into epoxyeicosatrienoic acids and HETEs. There are few studies regarding the potential role of lipids generated from P450 monooxygenase pathway in tumor biology. Therefore this review focuses on the involvement of COX and LOX in tumor initiation and progression.

3. CYCLOOXYGENASES IN TUMOR INITIATION AND PROGRESSION

3.1. Upregulation of COX expression in cancer.

Cyclooxygenase has two isoforms which differ mainly in their pattern of expression. COX-1 is widely expressed in most tissues, whereas COX-2 expression is usually absent but can be readily induced by numerous stimuli such as TNFα and phorbol ester. Aberrant or increased expression of COX-2 has been implicated in the pathogenesis of many diseases. It has been extensively documented that COXs, in particular the COX-2 isoform, are dysregulated in cancers, especially in colon cancer (11, 12). In addition to colon cancer, an elevation in COX-2 expression has been documented in pancreatic cancer (13, 14), lung cancer (15-18), gastric adenocarcinoma (19-21), breast cancer (22, 23), head and neck cancer (24, 25), and prostate cancer (26-28), among others (29, 30). The expression of COX-2 is determined by the genetic make-up of tumor cells. Oncogenes such as *ras* stimulate COX-2 expression (31), while tumor suppressors such as *p53* down-regulate COX-2 expression (32). Regarding COX-1, there are several studies suggesting its elevated expression in cancers such as ovarian (33).

3.2. Role of COX in tumor cell survival and proliferation

The acquisition of apoptosis resistance is one of the features of carcinogenesis. The induction of apoptosis in tumor cells, therefore, is a promising approach for inhibiting tumor growth. Selective inhibitors of COX-2 was found to inhibit the growth of human colon cancer (34), and also the growth of H-ras-transformed rat intestinal epithelial cells (35). Of the five primary prostaglandins, PGE_2 has been found to regulate apoptosis and BCL-2 expression in human colon cancer cells (36). In other cancers such as prostate cancer, it was found that NS398, a specific inhibitor of COX-2, could induce apoptosis in LNCaP cells in a time- and dose-dependent fashion. The induction of apoptosis was associated with a down-regulation in BCL-2 expression and with many apoptotic morphologic features such as chromatin condensation and chromosomal DNA fragmentation (37). In contrast, NS398 treatment had no effect on cell viability, nuclear function, or morphology in human fetal prostate fibroblasts (37). The study suggests a possible functional role of COX-2 in tumor cell resistance to apoptosis.

3.3. Role of COX in tumor angiogenesis and growth

Stimulation of capillary blood vessel ingrowth by tumors is a critical stage during tumor progression. Without tumor vasculature, the expansion of tumors is limited to several millimeters due to the limitation of oxygen and nutrient supply. Tumor cells can produce a number of growth factors and cytokines, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), to stimulate angiogenesis.

The role of COX-2 in tumor angiogenesis and growth was firstly implicated by the clinical and epidemiological data regarding the chemopreventive activities of non-steroid antiinflammation drugs (NSAIDs), which inhibit COX enzymatic activities, in colon cancer in nonfamilial adenomatous polyposis subjects. Further, NSAIDs induce a significant and often complete regression of colonic polyps in patients with familial adenomatous polyposis (38, 39). Further, ablation of COX-2 expression drastically suppressed the formation of interestinal polyps in Apc?716 knockout mice (40).

It has been shown that COX-2 plays a role in tumor angiogenesis and also in regulation of VEGF expression. In clinical breast tumor samples, the expression of COX-2 has been correlated with the expression of VEGF (41). A similar correlation between COX-2 expression and angiogenesis has been made in head and neck cancer (42). Increased expression of COX-2 in colon carcinoma stimulated endothelial cell migration and tube formation (43). Treatment with the select COX-2 inhibitor NS398 decreased the expression of VEGF and bFGF in COX-2 overexpressing colon cancer cells and inhibited tumor angiogenesis (44). These studies suggest that COX-2 regulates tumor angiogenesis and growth in colon cancer.

In other cancers such as prostate cancer, it was found that NS398 induced a sustained inhibition of PC-3 tumor cell growth and a regression of existing tumors (45). Immunohistochemical analysis revealed that NS398 had no effect on proliferation (PCNA), but induced apoptosis (TUNEL) and decreased microvessel density (angiogenesis). VEGF expression was also significantly down regulated in the NS398-treated tumors (45). Liu *et al* (1999) examined the relationship between COX-2 expression and VEGF induction in response to cobalt chloride-simulated hypoxia in three human prostate cancer cell lines (46). They found, in a human metastatic prostate cancer cell line, that VEGF induction by cobalt chloride-simulated hypoxia is maintained by a concomitant, persistent induction of COX-2 expression and sustained elevation of PGE_2 synthesis. Their results suggest that COX-2 activity, reflected by PGE_2 production, is involved in hypoxia-induced VEGF expression, and thus, modulates prostate tumor angiogenesis (46). A number of studies also implicated PGE_2 as an angiogenic factor (47, 48).

3.4. Regulation of tumor cell invasion and metastasis by COX products

It has been shown that COX-2 enhances the metastatic potential of colon cancer cells (49). Overexpression of COX-2 increased simultaneously the expression of matrix metalloproteinase and the invasion of colon cancer cells across Matrigel (49). In prostate cancer, Attiga and colleagues evaluated the effect of inhibitors of PLA2, COX, or LOX on the invasion of prostate tumor cells through Matrigel in vitro using the Boyden chamber assay and fibroblast-conditioned medium as the chemoattractant (50). They found that invasion through Matrigel was inhibited by the PLA2 inhibitor 4-bromophenacyl bromide, and the highly selective COX-2 inhibitor NS398. Inhibition of cell invasiveness by 4-bromophenacyl bromide (1.0 ? M), and NS398 (10.0 ? M) was reversed by the addition of PGE2 (50). PGE2 alone, however, did not stimulate invasiveness, which suggests that its production is necessary for rendering the cells invasive-permissive but not sufficient for inducing invasiveness (50).

3.5. COX-downstream enzymes in tumor initiation and progression

COX-2 has been regarding as a promising target of cancer prevention and treatment (51). However, some undesirable side effects, such as gastrointestinal bleeding, are associated with the use of NSAIDs (52). The use of COX-2 specific inhibitors for arthritic pain has been linked to an increased risk of cardiovascular events (53, 54). A better understanding of how COX applies to the biology of cancer is essential for developing mechanism-based prevention and treatment. Among five primary prostanoids, PGE2 is reported to promote tumor angiogenesis (55) and represents a novel angiogenic switch in mammary cancer progression (56). Recently it has been reported that in prostate cancer, thromboxane (TX) synthase is frequently up-regulated while its arachidonate product, TxA2, is involved in regulating tumor cell motility (57).

TX synthase converts the COX product PGH_2 to TxA_2. TxA_2 is rather labile, being hydrolyzed in aqueous solution with a half-life of about 30s to the biologically inactive thromboxane B_2 (TxB_2). This labile feature indicates that the availability of TxA_2 is tightly controlled and limited to the immediate vicinity of its production site. Increased levels of TxB_2 were observed in lung tumor tissues, when compared with non-tumor tissues (58). Increased TX synthase expression, or TxB_2 production, was also found in papillary thyroid carcinoma (59), larynx squamous cell carcinoma (60), and renal carcinoma (61).

The expression of TX synthase expression was examined in tumor tissues in comparison to their matched normal tissues using a cancer profiling array. Increased TX synthase expression at the mRNA level was found in 12 of 14 cases of renal carcinoma, 7 out of 9 cases of breast carcinoma, 2 out of 3 cases of prostate cancer, and 5 out of 7 cases of uterine cancer (57). The overall increase in TX synthase expression in tumor tissues suggests a potential role for this enzyme in tumorigenesis and progression of cancers.

In prostate cancer, the expression of TX synthase was increased in tumor specimens of advanced stage and grade, and particularly in the areas of perineural invasion (57). TX synthase expressed in prostate cancer cells was enzymatically active. When fed 1 μM of arachidonic acid, PC-3 cells produced 22.5 pg of TxB_2 per million cells a day. Treatment with 10 μM of carboxyheptal imidazole (CI), a selective inhibitor for TX synthase, reduced TXA_2 biosynthesis by 86%. Treatment of PC-3 cells with COX-1 specific inhibitor piroxicam reduced TxA_2 synthesis by 45 ~ 50%, while COX-2 specific inhibitor NS398 reduced TXA_2 production by 75 ~ 80%. Treatment of PC-3 cells with both COX-1 and COX-2 inhibitors eliminated TXA_2 production by 95%, comparable to that achieved by CI. The data suggest that TX synthase activity is dependent on COX-2, and to a lesser extent, COX-1, to supply the substrate PGH_2 (57).

Several studies suggest a potential involvement of TX synthase in tumor progression, especially tumor cell motility (62, 63). McDonough *et al* selected a population of cells from a long-term human astrocytoma cell line for their ability to migrate on a glioma-derived extracellular matrix (63), and this strain indeed showed enhanced migration rate as compared with the parental cells. Using differential display, they found that a 300-bp sequence homologous to TX synthase was up-regulated in the migration-selected cells relative to the parental cells, which was further confirmed by an RNase-protection assay and flow cytometry analysis, suggesting that an increase in TX synthase expression is associated with enhanced tumor cell migration (63). Inhibition of TxA_2 biosynthesis or functions was found to inhibit tumor cell migration (57) or trefoil peptide-stimulated cellular invasion (64).

4. ROLE OF 5-LIPOXYGENASE IN TUMOR PROGRESSION

4.1. Overview of 5-lipoxygenase

The enzyme 5-lipoxygenase (5-LO or 5-LOX) stereospecifically inserts molecular oxygen at carbon-5 of arachidonic acid, forming 5(S)-hydroperoxy-eicosatetraenoic acid (HpETE) (65). 5(S)-HpETE can be

reduced to 5(S)-HETE, which can further be dehydrogenated to 5-oxo-HETE. 5(S)-HpETE can also be utilized to generate the highly unstable allylic epoxide eicosatetraenoic acid or leukotriene (LT)A4, which can be further converted to LTB4 by LTA4 hydrolase, or LTC4 by LTC4 synthase, or lipoxin (LX) A4 and B4 by 12- or 15-LOX (2).). The 5-lipoxygenastion of aracidonic acid is the rate-limiting step in the biosynthesis of leukotrienes and lipoxins (2).

In humans, 5-LOX is physiologically expressed in cells of the myeloid lineage, B lymphocytes, and in the endothelial cells of the pulmonary artery. A putative role of 5-LOX is to regulate the immune inflammatory response. The bioactive lipid products from 5-LOX are important mediators of many inflammatory processes (2). LTB4 is a potent activator of neutrophil chemotaxis and trans-endothelial migration. Cys-LTs are key mediators of allergic inflammation. In addition, 5(S)-HETE and 5-oxo-HETE can activate neutrophils and/or monocytes.

4.2. Expression of 5-lipoxygenase in cancer

Elevated expression of 5-LOX, or its activating protein, has been described in a broad variety of cancer cells including colon, lung, breast, prostate, pancreas, bone, brain, and mesothelioma (66-70). Using 22 pair-matched benign and malignant tissue samples from same patients, Gupta *et al* (2001) found that both the expression and activities of 5-LOX were elevated in malignant tissue as compared with benign tissue (70). In breast cancer, aberrant expression of 5-lipoxygenase activation protein (FLAP) was found in aggressive tumors, whereas the levels of FLAP was found correlated with patient survival (66).

The mechanisms that selectively regulate the degree of 5-LOX gene expression remain elusive. Whether mutations of the 5-LOX promoter region occur in cancer and whether oncogenes induce transcription of 5-LOX remain to be investigated.

4.3. Role of 5-LOX in cell proliferation and survival

Inhibitors of 5-LOX or its activating protein, FLAP, have been reported to inhibit cell proliferation and induce apoptosis in various tumor cells, including prostate cancer (71). Anderson *et al* (1998) found that SC41661A and MK886, inhibitors of 5LOX cellular enzyme activity, reduced PC-3 prostate cell proliferation and with continued culture, induced apoptosis (72). Ghosh and Meyers (1998) further confirmed the ability of MK886 to induce apoptosis in prostate cancer cells (73). They found that MK886 completely blocked the biosynthesis of 5-HETE and induced massive and rapid apoptosis in LNCaP and PC-3 cells. Cells treated with MK886 demonstrated mitochondrial permeability transition between 30 and 60 min, externalization of phosphatidylserine within 2 hr, and degradation of DNA to nucleosomal subunits beginning within 2-4 hr (73).

In addition to prostate cancer, inhibitors of 5-LOX or FLAP also induced apoptosis in renal carcinoma (74), esophageal cancer (68), gastric cancer (75), pancreatic cancer (76), and breast cancer cells (77, 78). However, the precise mechanism of 5-LOX to promote cell survival is unclear. The activation of the stress response enzyme, JUN kinase, has been implicated in MK886 induction of apoptosis in prostate cancer (79). Recently a G-protein coupled receptor for 5-oxoETE, an archidonate metabolite of 5-LOX, has been found to be expressed in prostate cancer and may play a critical role in the survival of tumor cells(80). In addition to 5-oxoETE receptor, CysLT1 is highly expressed in colorectal adenocarcinomas and its degree of expression correlates negatively with patient survival (69). Recently, an interesting study found that 5-LOX antagonized P53 nuclear trafficking (81). Judging by the putative role of P53 in the apoptosis of cells after genotoxic stresses, it would be very interesting to study whether there is any alteration in apoptotic response of tumor cells with different P53 profiles when treated with MK886 or other 5-LOX inhibitors.

5. ROLE OF 12-LIPOXYGENASE IN HUMAN PROSTATE CANCER PROGRESSION

5.1. Upregulation of 12-LOX expression in cancer

12-LOX was found to be expressed in a variety of tumor cells. The mRNA of 12-LOX has been detected in erythroleukemia, colon carcinoma, epidermoid carcinoma A431 cells, human glioma, and breast cancer cells (82). Rat and murine tumor cell lines also express 12-LOX (83, 84). The cDNA sequence of endogenous 12-LOX from human epidermoid A431 cells was found to be identical to platelet-type 12-LOX (83, 84). The product of 12-LOX activity in tumor cells has been identified predominantly as the S enantiomer by chiral HPLC with its structural confirmation by GC-MS spectral analysis (85). In addition, 12-LOX mRNA has been found to be up-regulated in certain cancer cell lines by cytokines, such as epidermal growth factor and autocrine motility factor (86). In prostate cancer, Gao and co-authors investigated the expression pattern of 12-LOX at the mRNA level in 122 matching prostate normal and cancerous tissues by quantitative reverse transcription-PCR and analyzed for the possible association between 12-LOX expression and histologic grade, pathologic and clinical stage, margin positivity, age, and race (87). When compared with the matching normal tissues, 46 (38%) of 122 evaluable patients showed elevated levels of 12-LOX mRNA in prostate cancer tissues. A significantly greater number of cases were found to have an elevated level of 12-LOX among T3, high grade, and surgical margin-positive than T2, intermediate, and low grade, and surgical margin-negative prostatic adenocarcinomas. The study suggests that an elevation of 12-LOX mRNA expression occurs more frequently in advanced stage, high-grade prostate cancer (87).

5.2. Pro-angiogenic activity of 12-LOX in tumor growth

When overexpressed in breast or prostate cancer, 12-LOX was found to stimulate angiogenesis and tumor growth (88, 89). In the animal model, 12-LOX-overexpressing PC-3 cells formed larger tumors than did the vector controls(89), due to increased angiogenicity in 12-LOX overexpressing tumor cells as assessed by endothelial cell migration and Matrigel implantation assays (89). A similar observation regarding the role of 12-LOX

in tumor growth and angiogenesis was also observed independently by Connoly and Rose (1998) in breast cancer (88). The proangiogenic activity of 12-LOX may be due to the ability of its eicosanoid product, 12(S)-HETE, to stimulate endothelial cell migration and also elaborate the expression of angiogenic factors such as vascular endothelial growth factor and basic fibroblast growth factor (90).

5.3. Role for 12-LOX in cell proliferation and survival

Several studies have implicated 12-LOX as a regulator for tumor cell proliferation and survival. Initially Tang reported that inhibitors of 12-LOX or ablation of 12-LOX using antisense oligos induced apoptosis in rat Walker 235 cells (91). The induction of apoptosis by 12-LOX inhibitors was confirmed in prostate, breast, and various other cancer cells (92, 93). It was further found that inhibition of 12-LOX caused cell cycle arrest and reduced cellular proliferation in prostate cancer cells prior to apoptosis (94).

It should be noted that 12-LOX also has a pro-apoptotic function in neurons. Blockade or inhibition of 12-LOX was found to promote the survival of neuron cells under various external stresses (95, 96). In neuoblastoma cells, 12-LOX was found to mediate apoptosis (97). In addition, 12-LOX also had pro-apoptotic functions via lipid peroxide in fibroblasts (98). Therefore, the regulation of cell proliferation and survival by 12-LOX is dependent upon cellular context or the availability of different downstream effectors, which need to be further elucidated.

5.4. Role for 12-LOX in tumor cell invasion and metastasis

Overexpression of 12-LOX was found to increase metastatic potential of prostate cancer cells by affecting cytoskeleton and cellular motility, and local tissue invasion *in vivo* (99). In breast cancer, increased expression of 12-LOX stimulated the expression of matrix metalloproteinases (88). The pro-metastatic feature of 12-LOX may be related to its eicosanoid product, 12(S)-HETE, as it has been reported that 12(S)-HETE augments tumor cell metastatic potential. For example, 12(S)-HETE is found to modulate several parameters related to the metastatic potential of tumor cells, such as motility (100, 101), secretion of lysosomal proteinases cathepsin B and L (102), expression of integrin adhesion receptor (103), tumor cell adhesion to endothelium and spreading on subendothelial matrix (104), and lung colonizing ability *in vivo* (105).

6. PARADOXICAL ROLE FOR 15-LIPOXYGENASE-1 IN TUMOR INITIATION AND PROGRESSION

6.1. Pattern of 15-lipoxygenase-1 expression in tumor

Human 15-LOX-1 is the homolog of murine leukocyte 12-LOX (Leu-12-LOX), and unlike many other members of LOX, the substrate requirement of 15-LOX-1 is quite promiscuous. It can utilize arachidonic acid to form 15(S)-HETE and to a lesser extent, 12(S)-HETE. 15-LOX-1 can also utilize linoleic acid to form 13-(S)-hydroxyoctadecadienoic acid (13-HODE). In addition, 15-LOX-1 can oxygenate PUFAs in esterified form. In prostate cancer, the expression of 15-LOX-1 in both LNCaP and PC-3 cells was reported by Spindler *et al* (1997) using Western blot and RT-PCR (106). They developed a polyclonal antibody specific for 13-(S)-HODE and used this antibody to detect bioactive lipid in human prostate tumor specimens. They observed immunohistochemically detectable 13-HODE in human prostate cancer, whereas adjacent normal tissue showed no immunoreactivity (106).

The expression of 15-LOX-1 was found to be regulated by the tumor suppressor p53 (107). Kelavkar *et al* (2000) examined the expression of 15-LOX-1 and mutant p53 (mtp53) in human prostatic tissues in 48 prostatectomy specimens of different Gleason grades (n = 48) using immunostaining with antibodies specific for 15-LOX-1 and mtp53 (107). They found that 15-LOX-1 was located in secretory cells of peripheral zone glands, prostatic ducts and seminal vesicles, but not in the basal cell layer or stroma. Interestingly, robust staining in cancer foci for both 15-LOX-1 (36 of 48, 75%) and mtp53 (19 of 48, 39%) was noted. Furthermore, the intensities of expression in 15-LOX-1 and mtp53 correlated positively with each other ($P < 0.001$) and with the degree of malignancy, as assessed by Gleason grading ($P < 0.01$) (107).

The expression of 15-LOX-1 in secretory or differentiated epithelial cells of the prostate is congruent with the pattern of 15-LOX-1 in colon cells to a certain extent. Upon induction of terminal differentiation in Caco-2 cells by sodium butyrate treatment, 15-LOX-1 expression was stimulated (108). However, in contrast to the case of prostate cancer, 15-LOX-1 expression or activity was decreased in human colon cancers when compared with matched normal tissues (108, 109). The induction of 15-LOX-1 expression by sodium butyrate may be due to inhibition of histone deacetylase (HDAC). Eling and his group examined the expression of 15-LOX-1 in colorectal carcinoma Caco-2 and SW-480 cell after treatment with additional HDAC inhibitors such as trichostatin A and HC toxin. They found that HDAC inhibitors stimulated the gene expression of 15-LOX-1 and suggested that the level of 15-LOX-1 can be used as a marker to reflect histone acetylation in colorectal carcinoma (110).

In addition to histone acetylation, it has been reported that the status of methylation of CpG islands in the 15-LOX-1 promoter region determines the gene expression of 15-LOX-1 (111). The promoter region of 15-LOX-1 was methylated in all examined cells incapable of expressing 15-LOX-1, including certain solid tumor and human lymphoma cell lines and human T lymphocytes. In the human airway epithelial cell line A549 and human monocytes where 15-LOX-1 expression is IL-4-inducible, the promoter region of 15-LOX-1 was unmethylated (111). Inhibition of DNA methylation in L428 lymphoma cells was found conducive to 15-LOX-1 expression after IL-4 treatment (111). It is unknown, however, whether NSAIDs, which stimulate 15-LOX-1 expression in tumor cells, particularly colon cancer, affect the methylation of 15-LOX-1 promoter region or histone acetylation.

6.2. The tumor promoting activities of 15-lipoxygenase-1 in prostate cancer

In a transgenic model for prostate cancer (LPB-Tag), it was found that as mouse prostate progress to high grade prostatic intraepithelial neoplasia (HGPIN), 12(S)-HETE biosynthesis was increased four-fold (112). The results of QTRT and immunostaining revealed that the level of 12/15-LOX, the leukocyte-type 12-LOX (the murine homologue of human 15-LOX-1), was increased in neoplastic epithelial expression. Further, immunostaining showed the presence of Leu-12-LOX, the murine homolog of human 15-LOX-1, in invasive carcinoma and approximately one-half of metastatic foci (112). In another transgenic mouse model, the Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) model for prostate cancer, a similar observation was made regarding the expression and activities of murine Leu-12-LOX (113). The two studies suggest a potential role for 12/15-LOX in prostate carcinogenesis.

Kelavkar *et al* (2000) examined the role of 15-LOX-1 in PC-3 cell growth *in vitro* and *in vivo* (114). The proliferation rates of PC-3 cells were correlated with the level of 15-LOX-1 present. The 15-LOX-1 inhibitor, PD146176, demonstrated a dose-dependent inhibition of proliferation. In addition, overexpression of 15-LOX-1 enhanced the ability of PC-3 cells to grow in an anchorage-independent manner in a soft agar colony formation assay. Further, they found that PC-3 cells with high levels of 15-LOX-1 formed tumors more frequently and gave rise to larger tumors, than did their vector controls or PC-3 parental cells. This study suggests a causal role of 15-LOX-1 in prostate tumor growth and progression (114). The stimulation of tumor growth by 15-LOX-1 in PC-3 cells seems to be related to the stimulation of mitogenic signaling axis of insulin-like growth factor-1 (115). In addition, 15-LOX-1 also stimulated the expression of a putative angiogenic factor, vascular endothelial growth factor, in PC-3 cells (114).

6.3. The potential tumor suppressing activities of 15-lipoxygenase-1 in colon cancer

In contrast to the tumor-promoting activities of 15-LOX-1 in prostate cancer, a number of studies have demonstrated that 15-LOX-1 may act as a negative regulator in colon cancer via affecting apoptosis and terminal differentiation of colonic epithelial cells. In colon cancer cells treated with NSAIDs, 15-LOX-1 expression and activity were stimulated (116). The upregulation of 15-LOX-1 in NSAID-induced apoptosis seems mediated by the downregulation of GATA-6 transcription factor (117, 118). During apoptosis and differentiation of Caco-2 cells induced with sodium butyrate treatment, 15-LOX-1 was stimulated and the biosynthesis of 13(S)-HODE was increased (108, 119). Overexpression of 15-LOX-1 in Caco-2 cells was sufficient to cause apoptosis in Caco-2 cells (108), suggesting that 15-LOX-1 may act as a down-stream effector for NSAIDs or sodium butyrate in the induction of apoptosis. A weakened tumorigenic potential was documented in HCT-116 cells with overexpression of 15-LOX-1 when xenografted into animal models (120). The above studies suggest that 15-LOX-1 is associated with apoptosis or terminal differentiation of colon cancer cells, and therefore, may function as a tumor suppressor for colon cancer.

The pro-apoptotic activity of 15-LOX-1 may be partially due to its linoleate product, 13(S)-HODE. Shureiqi and colleagues found that 13(S)-HODE seems to act as an antagonist of peroxisome proliferator-activated receptor δ (PPARδ), a promoter of colonic tumorigenesis, by binding to PPAR-δ and decreasing its activation (121). In addition to PPARδ, P53 is implicated in the growth arrest or apoptotic signaling of 15-LOX-1 in colon cancer cells (122).

7. 15-LIPOXYGENASE-2 IN TUMOR INITIATION AND PROGRESSION

7.1. Loss of 15-lipoxygenase-2 expression in tumors

Originally cloned from human hair rootlets, human 15-LOX-2 has approximately 40% sequence identity to the known human 5-LOX, 12-LOX, and 15-LOX-1 (123). In contrast to 15-LOX-1, which prefers linoleic acid as the substrate to form 13(S)-HODE, 15-LOX-2 uses arachidonic acid exclusively to form 15(S)-HETE (123). The expression of 15-LOX-2, as evaluated by immunohistochemistry, is found mainly restricted to the prostate, lung, skin, and cornea (124).

The expression of 15-LOX-2 is found silenced during prostate carcinogenesis. In normal or benign prostate tissues, 15-LOX-2 expression is located in the secretory or luminal cells of peripheral zone glands and large prostatic ducts, and somewhat less uniformly in apical cells of transition and central zone glands (125). However, in prostate tumors, 15-LOX-2 immunostaining was completely absent in 23 of 70 cases, with negative staining in more than 50% of the tumor in 45 of 70 cases. Data from a number of clinical studies establishes that, in contrast to its uniform expression in differentiated secretory cells of benign prostate, the expression levels of 15-LOX-2 are inversely correlated with the pathological grade and Gleason scores of cancer patients(125-127).

In addition to prostate carcinogenesis, 15-LOX-2 expression is also repressed in lung neoplasm (128), skin-derived sebaceous neoplasms or carcinoma (126), and esophageal cancer (129).

Tang and his colleagues investigated the mechanism of silencing in 15-LOX-2 within prostate cancer cells (130). Cloning and analysis of the 15-LOX-2 promoter revealed that Sp1 positively, while Sp3 negatively, regulates the promoter activities of 15-LOX-2 in prostate epithelial cells (131). Neither hypermethylation of the promoter region of 15-LOX-2 or histone deacytylation, was a significant cause of 15-LOX-2 silencing in prostate cancer cells (130).

7.2. 15-Lipoxygenase-2 as tumor suppressor for prostate cancer

Increased expression of 15-LOX-2 was found related to replicative senescence in normal prostate

epithelial cells (132). Restoration of 15-LOX-2 in prostate cancer cells was found to inhibit DNA replication as indicated by a decrease in BrDU incorporation of cells with 15-LOX-2 expression (130). Tang and his colleagues identified 15-LOX-2 as a functional tumor suppressor in PC-3 cells (133). The conclusion is based upon the observation that PC-3 cells stably transfected with a 15-LOX-2 expression construct had diminished tumor development when injected into a mouse prostate (133). It is unknown whether 15-LOX-2 expressing PC-3 cells failed to form tumors or if the tumors derived grew smaller and slower than those derived from control PC-3 cells.

7.3. Intracellular signaling of 15-LOX-2: Is PPARg a downstream effector for 15-LOX-2?

Little is known about the potential intracellular signaling, stimulated by 15-LOX-2, which leads to the inhibition of cell cycle progression or tumor development. The eicosanoid product of 15-LOX-2, 15(S)-HETE, is a ligand for peroxisome proliferator-activated receptor γ (PPARγ) (134). The ligand, 15(S)-HETE, has been demonstrated to inhibit prostate cancer cell growth, and at the concentration of 20 μM or above, induce apoptosis (130, 135), presumably through activation of PPARγ (136). Agonists of PPARγ such as rosiglitazone, have been demonstrated to induce apoptosis in cancer cells, most notably in cancer of the prostate. Further, oral administration of troglitazone produced significant inhibition of PC-3 tumor growth ($P = 0.01$) in immunocompromised mice (52).

Shappell *et al* (2001) investigated whether 15(S)-HETE modulates proliferation of PC-3 cells through a PPARγ-dependent pathway (135). 15(S)-HETE dose-dependently inhibited PC-3 growth on soft agar with IC_{50} of 30 μM. 15(S)-HETE could cause an approximately 2-3 fold increase in PPARγ-dependent transcription (135). The study suggests that 15-LOX-2-derived 15(S)-HETE may function as an endogenous ligand for PPARγ in the prostate. Therefore, reduced expression of 15-LOX-2 and reduced endogenous production of 15(S)-HETE may contribute to increased proliferation and reduced differentiation in prostate carcinoma (135).

However, the enzymatic activity of 15-LOX-2 seems dispensable for its tumor suppressing activities. PC-3 cells transfected with a splice variant of 15-LOX-2, 15-LOX-2sv-b, which did not have the capacity of synthesizing 15(S)-HETE, also had reduced tumor development (133). This evidence suggests that 15(S)-HETE biosynthesis is dispensable for 15-LOX-2 to exert tumor suppressing activities. A recent study from Mentor and colleagues suggest that 15-LOX-2 and PPARγ expressions are inversely correlated: When 15-LOX-2 expression is lost, PPARγ level is increased; conversely, when 15-LOX-2 expression is restored, PPARγ expression is reduced (137). Genetic ablation of PPARγ did not have a discernible effect on prostate cancer development in an animal model (138). Clearly other pathways, independent of PPARγ, can be activated by 15-LOX-2 in exerting its tumor suppressing activities with regards to prostate cancer.

8. CONCLUSIONS AND PERSPECTIVE

The expression of COX and LOX are dysregulated in cancers. It has been shown in many studies that COX-2 expression is upregulated in various cancers. Inhibitors of COX-2 have been found to inhibit tumor cell proliferation, invasion, angiogenesis and tumor growth. Further studies are needed to elucidate which downstream enzyme(s) of COX can recapitulate the tumor promoting activities of COX-2. Among many members of LOX family, a number of studies suggest that 5-LOX and 12-LOX can promote tumor initiation or progression. In contrast, 15-LOX-2 is strongly implicated as a negative regulator of carcinogenesis in the prostate. Future studies are needed to assess whether 15-LOX-2 can also function as a tumor suppressor in lung, esophageal, and other cancers in which 15-LOX-2 expression is found silenced during carcinogenesis.

Regarding 15-LOX-1, its paradoxical roles in prostate and colon carcinogenesis are intriguing. On one hand, 15-LOX-1 seems to act as a tumor promoter in prostate cancer, as evidenced by the observations that 15-LOX-1 expression is elevated in cancer of the prostate in direct correlation with the presence of mutant P53, and that it stimulates prostate cancer cell growth *in vitro* and tumor growth *in vivo*. On the other hand, in colon cancer, 15-LOX-1 seems to function as a tumor suppressor. 15-LOX-1 has been identified as a downstream effector for NSAID-induced apoptosis and butyrate-induced terminal differentiation in colon cancer cells. Furthermore, 15-LOX-1 expression and activity are downregulated in colon cancer as compared to its matched normal tissues. These intriguing findings mandate further studies to elucidate the exact functional roles played by 15-LOX-1 in cancer biology.

9. ACKNOWLEDGMENT

This work was supported by United States Army Research Programs W81XWH-04-1-0749 and W81XWH-04-1-0143, and an award from Illinois Department of Public Health. Due to space limitation, the author apologizes for any pertinent studies not cited in this article.

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Abbreviations: bFGF, basic fibroblast growth factor; CI, carboxyheptal imidazole; COX, cyclooxygenases; FLAP, 5-lipoxygenase activation protein; HDAC, histone deacetylase; HETEs, hydroxyeicosatetraenoic acids; HGPIN, prostatic intraepithelial neoplasia; 13-HODE, 13-(S)-hydroxyoctadecadienoic acid; HpETE, hydroperoxy-eicosatetraenoic acid; LO or LOX, lipoxygenases; LT, leukotriene; LX, lipoxin; NSAIDs, non-steroid antiinflammation drugs; PG, prostaglandin; PGHS, prostaglandin H_2 synthases; PGI_2, prostacyclin; PLA_2, phospholipase A_2; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acids; TRAMP, transgenic Adenocarcinoma of Mouse Prostate; TX, thromboxane; TxA_2, thromboxane A_2; VEGF, vascular endothelial growth factor

Key Words: Cyclooxygenase, Lipoxygenase, Eicosanoid, Tumor Progression, Apoptosis, Angiogenesis

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