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Perspectives in Cancer Research

Lipoxygenase Modulation to Reverse Carcinogenesis[1]

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Abstract

New studies of the relationship between polyunsaturated fatty acid metabolism and carcinogenesis have led to novel molecular targets for cancer chemoprevention research. These targets include procarcinogenic lipoxygenases (LOXs), including 5-, 8-, and 12-LOX, and anticarcinogenic LOXs, including 15-LOX-1 and possibly 15-LOX-2. Recent studies indicate that 15-LOX-1 is down-regulated in colorectal cancer cells and that the ability of nonsteroidal anti-inflammatory drugs, a class of clinically active cancer chemopreventive agents, to induce apoptosis and growth inhibition in these cells was dependent on the induction of 15-LOX-1 and its metabolic product 13-*S*-hydroxyoctadecadienoic acid. Consistent with the colorectal studies, 15-LOX very recently has shown anticarcinogenic activity in esophageal and prostatic carcinogenesis. Inhibitors of other LOXs (*e.g.*, 5-LOX) have preclinical anticarcinogenic activity and are being developed for clinical chemoprevention study. These and other LOX data led us to propose that the various LOX pathways exist in a dynamic balance that shifts during carcinogenesis toward 5-, 8-, and 12-LOX (and cyclooxygenase-2) and away from 15-LOX. A novel approach for cancer chemoprevention would involve LOX modulators, *i.e.*, agents that can induce the anticarcinogenic and/or inhibit the procarcinogenic LOXs, thereby shifting the balance of LOX activities from procarcinogenic to anticarcinogenic metabolism of polyunsaturated fatty acids.

Introduction

The molecular study of the well-known relationship between polyunsaturated fatty acid metabolism and carcinogenesis is revealing novel molecular targets for cancer chemoprevention research. Polyunsaturated fatty acids can enhance tumorigenesis in animal models. Certain agents, including NSAIDs,[3] have demonstrated cancer chemopreventive effects associated with their ability to modulate polyunsaturated fatty acid metabolism. Recently discovered molecular targets within polyunsaturated fatty acid metabolism are especially relevant to NSAID activity in colorectal and other sites of carcinogenesis.

The COXs and LOXs are two important enzyme classes that metabolize polyunsaturated fatty acids and affect carcinogenesis (Fig. 1). The LOXs convert arachidonic, linoleic, and other polyunsaturated fatty acids into biologically active metabolites that influence cell signaling, structure, and metabolism (1). In the classic pathway involving only arachidonic acid (the eicosanoid-generation pathway), arachidonic acid is a substrate for both LOX and COX enzymes to form various metabolites, such as HETEs (5-, 8-, 12-, and 15-*S*-HETE) and prostaglandins (2). As with arachidonic acid, linoleic acid, which is the predominant polyunsaturated fatty acid in the human diet (3), can undergo oxidative metabolism. In contrast to the multiple oxidative metabolic pathways for arachidonic acid, the oxidative metabolism of linoleic acid in humans mainly is limited to the 15-LOX-1 pathway, which produces 13-*S*-HODE (4, 5).

Initially, the enzyme COX-2 and its inhibition were thought to be the major, if not only, target and mechanism of NSAID effects in colorectal and other sites of carcinogenesis. It now is understood that other molecular targets besides COX-2 are involved (6, 7), *e.g.*, NSAIDs can trigger apoptosis as a chemopreventive mechanism in colon cancer cells through the up-regulation of 15-LOX-1 (8) and down-regulation of PPAR-δ (9).

This article presents a new perspective on the dynamically evolving research into the differing roles of the known LOXs and their metabolic products in carcinogenesis and chemoprevention. One group of LOXs, including 5-, 8-, and 12-LOX, has procarcinogenic roles and appears to work mainly within the arachidonic acid pathway. Two isoenzymes of 15-LOX, however, have anticarcinogenic roles and work either in the linoleic or arachidonic acid pathway. The anticarcinogenic isoenzymes 15-LOX-1 and -2 have become the focus of very recent molecular targeting study, especially with respect to 15-LOX-1 in the colon.

Polyunsaturated Fatty Acids, LOX Metabolism, and Carcinogenesis

Early tumorigenesis studies in animals showed that dietary fats enhance carcinogenesis through a structure containing polyunsaturated bonds (10) and the n-6 function (n is the first unsaturated function from the methyl terminal group; Ref. 11), *e.g.*, n-6 polyunsaturated fatty acids (*e.g.*, arachidonic and linoleic [through conversion to arachidonic] acids; Fig. 1) promote tumorigenesis, whereas n-3 polyunsaturated fatty acids (*e.g.*, those found in fish oil) have antitumorigenic effects in animal models (12–14).

Later tumorigenesis studies demonstrated that polyunsaturated fatty acids must undergo oxidative metabolism to enhance tumorigenesis (15–17). The LOXs and COXs mediate the oxidative metabolism of linoleic and arachidonic acids in forming an array of biologically active metabolites, such as prostaglandins, HETEs, and HODEs. Various LOX products have been linked to tumorigenesis *in vitro* and *in vivo* in experimental models, and the modulation of LOX metabolism has anticarcinogenic effects in these models (18–20). Therefore, the oxidative metabolism of n-6 polyunsaturated fatty acids has been targeted for developing anticarcinogenic interventions, such as with the natural products curcumin and polyphenols, which modulate LOX activity and have promising results in preclinical carcinogenesis studies (21, 22). Synthetic LOX inhibitors that were developed originally for treating inflammatory diseases (23) also have antitumorigenic effects in preclinical models (24).

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[3] The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; LOX, lipoxygenase; COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; 13-*S*-HODE, 13-*S*-hydroxyoctadecadienoic acid; PPAR, peroxisome proliferator-activated receptor; LT, leukotriene; FLAP, 5-LOX-activating protein; EGF, epidermal growth factor.

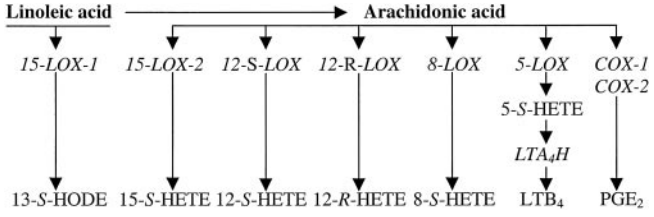

Fig. 1. Polyunsaturated fatty acid metabolic pathways of arachidonic acid and linoleic acid through LOXs and COXs.

Procarcinogenic LOX Metabolism of Arachidonic Acid

Several LOXs form different metabolites within the arachidonic acid pathway that appear to enhance tumorigenesis. These LOXs and metabolites include 5-LOX and its products 5-*S*-HETE and LTB_4; 8-LOX and 8-*S*-HETE; 12-*S*-LOX and 12-*S*-HETE; and 12-*R*-LOX and 12-*R*-HETE. Although 15-LOX-2 also metabolizes arachidonic acid to form 15-*S*-HETE, recent data suggest that this LOX and product may be anticarcinogenic, and they are discussed later.

5-LOX and Its Products 5-*S*-HETE and LTB_4. 5-LOX converts arachidonic acid to 5-*S*-HETE, which in turn is converted to LTA_4 and then to LTB_4 by LTA_4 hydrolase (25). This process requires the activity of the additional enzyme FLAP, which activates 5-LOX (26) and the translocation of 5-LOX into the nuclear membrane (27).

Several studies have suggested a link between 5-*S*-HETE formation and carcinogenesis in various organs. Prostate, lung, and other cancer cell lines express 5-LOX and FLAP mRNA (28, 29). 5-LOX overexpression recently has been documented in human prostate cancer tissue (30), and 5-*S*-HETE formation and inhibition respectively promote and inhibit the growth of prostate cancer cells (31). 5-*S*-HETE but not other HETE products (LTB_4, 12-, or 15-HETE) can also inhibit apoptosis induction by MK-886 (a specific FLAP inhibitor) in prostate cancer cell lines (32). Similarly, 5-LOX metabolism of arachidonic acid promotes the growth of lung cancer cells, and 5-LOX inhibitors suppress cell proliferation and induce apoptosis in a variety of these cell lines (29). 5-LOX and FLAP inhibitors can reduce tumorigenesis induction by 4-methylnitrosamino-1-(3-pyridyl)-1-butanone, a tobacco carcinogen (33). Ding *et al.* (34) found that 5-LOX mRNA is expressed in pancreatic cancer but not in normal pancreatic cells. They confirmed the specific mechanistic role of 5-LOX in promoting pancreatic cancer cell proliferation by blocking 5-LOX expression with an antisense method, which inhibited proliferation, and then adding back 5-*S*-HETE, which reversed the beneficial effects of 5-LOX inhibition. 5-LOX inhibitors also can inhibit the growth of mouse colon adenocarcinoma cell lines *in vitro* and *in vivo* (19, 20).

Not all studies, however, support the view that 5-LOX contributes to carcinogenesis. The naturally occurring carcinogen 1-hydroxyanthraquinone induces tumorigenesis in rat colon mucosa without affecting 5-LOX expression (35). The 5-LOX inhibitor acetyl-11-keto-β-boswellic acid induces apoptosis in cells that lack 5-LOX expression, possibly through topoisomerase I inhibition (36). The FLAP inhibitor MK-886 induces apoptosis in human chronic lymphocytic cancer cells lacking FLAP expression. Down-regulating FLAP expression by an antisense method in cells expressing FLAP had the minor effect of increasing the percentage of apoptotic cells from 4.4 to 10.7% (37). Therefore, although the role of 5-LOX in promoting prostate, lung, and pancreatic carcinogenesis is strongly supported by experimental data, 5-LOX may not promote carcinogenesis in all models.

LTB_4 is a more terminal product of the 5-LOX metabolic pathway than is 5-*S*-HETE. LTB_4 inhibits apoptosis (38) and has been shown to be procarcinogenic in several studies. The tobacco carcinogen 4-methylnitrosamino-1-(3-pyridyl)-1-butanone increased plasma LTB_4 in animal lung tumorigenesis (33). Bortuzzo *et al.* (18) studied the effects of LTB_4, LTB_4 methyl ester, LTB_5, 12-*R*-HETE, 12-*S*-HETE, and 15-*S*-HETE on the colon cancer cell lines HT-29 and HCT-15. Only LTB_4 and 12-*R*-HETE (a 12-*R*-LOX and cytochrome P450 product of arachidonic acid) stimulated colonic cell proliferation. SC-41930, a competitive antagonist of LTB_4, blocked the LTB_4 effects. Findings from the same laboratory, however, indicated that the LTB_4 levels in surgical samples of 21 colon cancer patients and paired normal tissue were not significantly different (39). One possible explanation for this finding is that the normal surgical samples may have contained substantial amounts of connective tissue and inflammatory cells containing LTB_4 that confounded the results.

Other evidence also supports a pro-tumorigenic effect of LTB_4. *In vitro*, colon cancer cells produce LTB_4 (40), and LTB_4 synthesis can be triggered by putative tumorigenic agents, such as bile salts (41). *In vivo*, LTB_4 levels are increased in intestinal tumors *versus* in normal appearing intestinal mucosa of mice, and the NSAID sulindac blocks this increase (42).

8-LOX and 8-*S*-HETE. Compared with other LOXs, 8-LOX has received little attention for its role in carcinogenesis. Recent findings, however, suggest that 8-LOX enzymatic activity increases dramatically in early stages of mouse skin tumorigenesis (43) and that 8-LOX up-regulation in mice promotes skin carcinogenesis (44). Additionally, 8-*S*-HETE has genotoxic effects that might contribute to the development of the mutator phenotype of tumor cells (43). Recently reported data show 78% homology between 8-*S*-LOX in mice and 15-LOX-2 in humans. Despite this resemblance, the products of 8-LOX and 15-LOX-2 are quite different (45) and so possibly have distinct roles in carcinogenesis. The human *8-LOX* gene has not been cloned, however. Other recent work has identified the 8-LOX-product 8-HETE in humans (8).

12-*S*-LOX and 12-*S*-HETE. Several lines of evidence indicate that the 12-*S*-LOX product 12-*S*-HETE contributes substantially to carcinogenesis (46). Platelet-type 12-*S*-LOX is one of three 12-*S*-LOX isoenzymes and is the one found in humans (46). The expressions of platelet-type 12-*S*-LOX mRNA and protein have been detected in prostate, melanoma, and some other cancer cell lines (47, 48). 12-*S*-LOX in tumor cells produces 12-*S*-HETE, and 12-*S*-HETE promotes such tumorigenic events as invasion and metastasis by: (*a*) up-regulating adhesion molecules (49); (*b*) increasing the adhesion of tumor cells to the matrix protein fibronectin (50) and microvessel endothelium (51); and (*c*) enhancement of cell migration during tumorigenesis (52) and promoting tumor spread (53) through modulation of protein kinase C-α (50, 51, 54). The stable transfection of 12-LOX-specific antisense into Walker 256 tumor cells induced apoptosis, which could be attenuated by adding 12-*S*-HETE (55). 12-*S*-HETE also contributes to the regulation of DNA transcription through a possible interaction between 12-*S*-HETE-binding receptor and steroid receptor coactivator-1, which also interacts with PPARs, retinoid X receptors, and other nuclear receptors (56).

These *in vitro* data have been extended by human and animal *in vivo* tumor studies. The degree of 12-*S*-LOX overexpression in human prostate cancer correlates with the tumor grade and stage (47). The relation of 12-*S*-LOX to tumor metastatic potential is additionally supported by the finding that 12-*S*-LOX expression levels were higher in metastatic prostate cancer cells (DU-145) than in nonmetastatic prostate cancer cells (PC-3) that were transplanted into severe combined immunodeficient mice (48). Besides being higher, the 12-*S*-LOX expression was also more localized in the cytoskeleton in DU-145 (metastatic) cells than in PC-3 (nonmetastatic) cells, and

12-*S*-LOX inhibition markedly reduced the metastatic potential of the DU-145 cells (48).

Additional *in vivo* data that support the role of 12-*S*-HETE in carcinogenesis include: (*a*) skin tumorigenesis in animal models results in platelet-type 12-*S*-LOX overexpression leading to an increase in 12-*S*-HETE production (57); (*b*) ectopically overexpressed platelet-type 12-*S*-LOX enhances tumorigenesis by promoting angiogenesis in human prostate cancer cells (52); and (*c*) overexpression of 12-*S*-LOX also can enhance an angiogenic response in normal endothelial cells (58).

12-*R*-LOX and 12-*R*-HETE. Initially thought to involve only cytochrome P450, 12-*R*-HETE production also involves 12-*R*-LOX, which recently has been cloned from human skin (59). Very limited data exist regarding the relationship between 12-*R*-HETE and tumorigenesis. Currently available information indicates that 12-*R*-HETE promotes the proliferation of colon cancer cell lines *in vitro* (18).

Anticarcinogenic LOX Metabolism of Arachidonic and Linoleic Acid

15-LOX-1 and -2 are two isoenzymes of 15-LOX that appear to exert important anticarcinogenic effects through the metabolism of polyunsaturated fatty acids. The preferred substrate for 15-LOX-1 is linoleic acid and for 15-LOX-2 is arachidonic acid (60).

15-LOX-1 and 13-*S*-HODE. Whereas several oxidative metabolites are formed from arachidonic acid, the main oxidative metabolite of linoleic acid in human cells is 13-*S*-HODE (4, 5). 15-LOX-1 is the main enzyme for metabolizing linoleic acid into 13-*S*-HODE (4, 61) and is the only 15-LOX isoenzyme found in the epithelium of the human colon (62).

Several early studies suggested that 13-*S*-HODE enhances cell proliferation. 13-*S*-HODE potentiates the mitogenic response to EGF in fibroblasts (63), Syrian hamster embryo cells (17), and breast cancer cells (BT-20; Ref. 64). The transfection of C-erbB-2 (a proto-oncogene similar to EGF receptor) into normal fibroblasts increases 13-*S*-HODE production (65). The activity level of 13-HODE dehydrogenase, which metabolizes 13-*S*-HODE to 13-oxo-octadecadienoic acid, decreases as colonic epithelial cells undergo malignant transformation (66). Therefore, it was proposed that the 15-LOX-1 product 13-*S*-HODE enhances colonic tumorigenesis (62) and that 13-HODE dehydrogenase counteracts this effect (66). These proposed effects, however, were inconsistent with other findings showing that 13-*S*-HODE did not enhance EGF-dependent DNA synthesis in transformed Syrian hamster embryo cells that had lost tumor suppressor gene function (67).

We have found that 13-*S*-HODE levels and 15-LOX-1 expression are reduced in human colorectal cancers (68). These findings suggested that the previously observed reduction in 13-*S*-HODE dehydrogenase levels in cancer cells (66) might be secondary to the reduction in 13-*S*-HODE levels. Several studies have also shown that 13-*S*-HODE is linked to cellular differentiation and apoptosis. 13-*S*-HODE attenuates ornithine decarboxylase activity in the rat colon (69) and reverses skin hyperproliferation in guinea pigs (70). Human osteosarcoma cells with enzymatically active 15-LOX-1 expression after transient transfection with human 15-LOX-1 grow slower by >50% than do osteosarcoma cells without enzymatically active 15 LOX-1 expression (71). The cell growth rates return to about that of nonexpressing clones when 15-LOX-1 expression is lost. 13-hydroxyperoxyoctadecadienoic acid, the immediate and transient precursor of 13-*S*-HODE, induces apoptosis in human T cells (72). The induction of differentiation causes the expression of 15-LOX-1 in Caco-2 colon cancer cells and human tracheobronchial epithelial cells, which is associated with linoleic acid conversion to 13-*S*-HODE (73, 74).

Additional *in vitro* mechanistic studies of 13-*S*-HODE effects on colorectal cancer cells support and extend our earlier findings in human colorectal tissue samples. 13-*S*-HODE induces apoptosis and cell cycle arrest in colorectal cancer cells (68). Therefore, 13-*S*-HODE is likely to have anti- rather than pro-tumorigenic effects, contrasting with the effects of the metabolites of 5-, 8-, and 12-LOXs. This concept is supported by the finding of others that linoleic acid inhibits rather than promotes carcinogenesis in a mouse-skin tumorigenesis model (75) wherein linoleic acid is not converted into arachidonic acid but is converted into 13-*S*-HODE (76).

We have studied the apoptotic effects of NSAIDs in relation to 15-LOX-1 expression in colorectal cancer cells to determine whether the induction of 15-LOX-1 can be targeted therapeutically in the colon (8, 77). We found that NSAIDs induce 15-LOX-1 expression in colorectal cancer cells and that 15-LOX-1 up-regulation is critical to NSAID induction of apoptosis (8). We also found that the induction of 15-LOX-1 expression and apoptosis by NSAIDs was independent of COX-2 inhibition (77).

The role of 15-LOX-1 in apoptosis also has been reported in human esophageal epithelia. We have recently found that 15-LOX-1 is down-regulated *in vitro* and *in vivo* in human esophageal cancers, and NSAIDs restore 15-LOX-1 to induce apoptosis in human esophageal cancer cells (78). Therefore, cancer cells appear to escape apoptosis in two common gastrointestinal cancers by down-regulating 15-LOX-1 expression and decreasing 13-*S*-HODE production. Chemopreventive NSAIDs clinically are active in colorectal (6) and promising in esophageal carcinogenesis (79), in which 15-LOX-1 appears to be a crucial molecular target for the apoptotic effects of NSAIDs (8, 77, 78). The study of the relationship between 15-LOX-1, NSAIDs, and apoptosis has not been reported for other organ systems.

15-LOX-2 and 15-*S*-HETE. The 15-LOX-2 enzyme converts arachidonic acid mainly into 15-*S*-HETE. 15-LOX-2 is expressed in some but not all normal human tissues (*e.g.*, cornea, prostate, lung, and skin; Ref. 60). 15-LOX-2 expression is reduced in human prostate carcinomas (80) and high-grade prostatic intraepithelial neoplasia (81). There are conflicting *in vitro* data, however, regarding the role of 15-*S*-HETE in carcinogenesis.

Some studies suggest that 15-*S*-HETE might have antitumorigenic effects, particularly by antagonizing other LOX products, such as LTB_4 and possibly 12-*S*-HETE. These effects include: (*a*) 15-HETE inhibits LTB_4 production (82, 83) and platelet-type 12-LOX activity (84) and reduces LTB_4 binding to its receptors and thereby cellular responses to LTB_4, such as cytoskeletal rearrangement and leukocyte trafficking through the endothelium (85); and (*b*) 15-*S*-HETE reduces 5-LOX activity in rat basophilic leukemia cells (86, 87).

Other studies have suggested that 15-*S*-HETE may suppress apoptosis (55, 88), has no effect on apoptosis in cancer cells (18, 89), or that 15-hydroperoxyeicosatetraenoic acid, the immediate precursor of 15-HETE, induces apoptosis in lymphocytes (72). A more recent study has shown that 15-*S*-HETE inhibits proliferation in PC3 prostate carcinoma cells possibly through activation of PPAR-γ (90). Although the balance of the evidence suggests that 15-*S*-HETE has an antitumorigenic role, this role requires confirmation in additional studies.

Theoretical Model for the LOX Dynamic Balance and Its Modulation

As summarized above, a group of LOXs joins COX-2 in promoting tumorigenesis by metabolizing arachidonic acid. Other LOXs (15-LOX-1 and -2) suppress carcinogenesis by metabolizing linoleic and

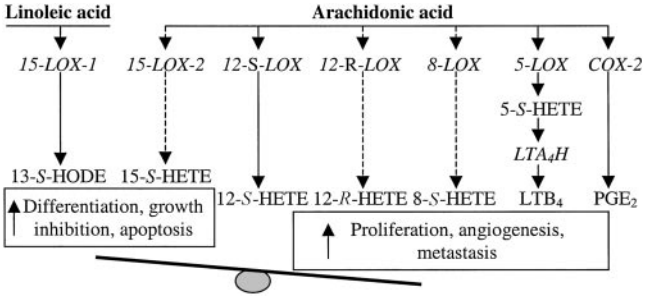

Fig. 2. A proposed dynamic balance among the polyunsaturated fatty acid metabolic pathways of arachidonic and linoleic acid through LOXs and COX-2 during tumorigenesis. Linoleic acid is the primary substrate for anticarcinogenic 15-LOX-1, whereas arachidonic acid is the primary substrate for procarcinogenic LOXs and 15-LOX-2, which may have anticarcinogenic effects. The imbalance indicated at the *bottom* of the figure suggests that the various LOX pathways exist in a dynamic balance that has shifted during carcinogenesis toward 5-, 8-, and 12-LOX (and COX-2) and away from 15-LOX. A novel approach for cancer chemoprevention would involve using LOX-modulating agents to tip the balance back toward 15-LOX metabolism of polyunsaturated fatty acids by inducing the anticarcinogenic and/or inhibiting the procarcinogenic LOXs. *Dotted arrows* associated with 15-LOX-2, 12-*R*-LOX, and 8-LOX reflect the limited available data on these enzymes with respect to carcinogenesis.

arachidonic acids, respectively. This dichotomy in overall LOX effects suggests that a dynamic balance exists among the various LOXs. We propose that the pro and anticarcinogenic LOXs exist in a dynamic balance that is shifted during tumorigenesis from the metabolic activity of 15-LOX promoting cell differentiation, growth inhibition, and apoptosis to the metabolic activities of other LOXs and COX-2 promoting tumorigenesis through arachidonic-acid metabolites, such as LTB_4, 12-*S*-HETE, and prostaglandin E_2 (Fig. 2). Until recently, LOX cancer chemoprevention research focused exclusively on the tumor-promoting effects of LOXs and on inhibiting LOX in general and 5- and 12-LOX in particular (24, 33). Now we know that LOXs, *i.e.*, 15-LOX-1 and -2, also can suppress tumorigenesis. Therefore, a novel approach for cancer chemoprevention would involve LOX modulators, *i.e.*, agents that can induce the anticarcinogenic and/or inhibit the procarcinogenic LOXs, thereby shifting the balance of LOX activities from procarcinogenic to anticarcinogenic metabolism of polyunsaturated fatty acids.

Several studies support the concept of a dynamic LOX balance. Antagonistic interactions may occur between 5- and 15-LOX and between 12- and 15-LOX in various experimental models, which involved direct effects of the 15-LOX-1 and -2 products (13-*S*-HODE and 15-HETE, respectively) on 5- and/or 12-LOX or their products (50, 82–87, 91). Interleukin-4, which can induce 15-LOX-1 up-regulation and apoptosis in cancer cells (92, 93), was shown very recently in a noncancer experimental system to have the dual effect of up-regulating 15-LOX-1 and inhibiting 5-LOX (94).

The extent to which the LOX dynamic balance is governed directly by alterations in the relative expression/activity of the various LOXs or by substrate shifts between linoleic and arachidonic acid or by both has yet to be defined. There are data supporting a direct regulation, such as the regulation of 15-LOX-1 at the transcriptional and post-translational levels in cancer cells (64, 95, 96). It is possible that: (*a*) inhibiting harmful LOXs will make more arachidonic- or linoleic-acid substrate available for the anticarcinogenic effects of 15-LOX-1 and -2; and (*b*) inducing 15-LOX-1 and/or -2 will make less substrate available for procarcinogenic LOX and COX-2 effects. In colorectal carcinogenesis, however, a substrate shift (away from COX-2) did not appear to be involved in the up-regulation of 15-LOX-1 by NSAIDs (77). These mechanistic issues, which are only just beginning to be assessed with respect to NSAID and LOX-inhibitor effects on the LOX dynamic in cancer cells, will require additional study.

Our proposed theoretical model of a dynamic LOX balance is based on data from studies of chemical inhibitors, comparative animal and human LOX expressions and enzymatic activities in normal and cancer tissues, inhibiting enzymes and adding back their products, and gene manipulation (overexpression or antisense) approaches to examine the specific roles of the various LOXs. Future study in these areas, including studies to develop more selective LOX inhibitors and more sensitive quantitative assessments of LOX activities/metabolites, will strengthen the theoretical model and our understanding of the roles of LOXs in carcinogenesis.

The ultimate goals of future LOX study include the validation of LOX targets and establishment of LOX modulators for the clinic. It will be important to clarify the mechanism(s) by which the modulation of various LOXs affects cell proliferation and apoptosis, which may involve PPARs (97). 13-*S*-HODE and 15-*S*-HETE (products of 15-LOX-1 and -2, respectively) activate PPAR-γ (97), which can lead to growth inhibition and apoptosis (88, 98). NSAIDs also can activate PPARs (99) and induce growth inhibition and apoptosis. Therefore, NSAID modulation of LOXs and subsequent anticarcinogenic effects may involve PPAR activities within the 15-LOX-1 signal-transduction pathway, because NSAIDs up-regulate 15-LOX-1 expression and enzymatic activity (8, 77, 78). The mechanisms involving 15-LOX-1, PPARs, and other NSAID targets are being worked out in high-concentration *in vitro* studies of NSAIDs (8, 9, 77, 78, 99), and this work is being extended to *in vivo* settings. The study of NSAIDs and other LOX modulators is intensifying. As foretold by the recent discoveries of 8-LOX, 12-*R*-LOX, and 15-LOX-2, future research may reveal new LOXs (100) and potentially new roles for known LOXs in the development and reversal of carcinogenesis.

Conclusion

LOX metabolism of linoleic and arachidonic acids leads to the formation of a variety of metabolically active products with different roles in carcinogenesis. Our understanding of these roles is steadily increasing. This increased understanding is helping to form a theoretical basis for developing new cancer chemoprevention approaches targeted on LOX activity within the polyunsaturated fatty acid metabolic pathway. The differential roles for the various LOXs during tumorigenesis should be incorporated within the theoretical framework of novel cancer chemoprevention strategies (101).

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