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15-lipoxygenase-1 as a tumor suppressor gene in colon cancer: is the verdict in?

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Abstract

15-Lipoxygenase-1 (15-LOX-1) is an inducible and highly regulated enzyme in normal human cells that plays a key role in the production of lipid signaling mediators, such as 13-hydroxyoctadecadienoic acid (13-HODE) from linoleic acid. 15-LOX-1 significantly contributes to resolution of inflammation and to terminal differentiation of normal cells. 15-LOX-1 is downregulated in human colorectal polyps and cancers. Emerging data support a tumor suppressor role for 15-LOX-1, especially in colon cancer. These data indicate that 15-LOX-1 promotes various antitumorigenic events, including cell differentiation and apoptosis, and inhibits chronic inflammation, angiogenesis, and metastasis. The transcriptional repression of 15-LOX-1 in colon cancer cells is complex and involves multiple mechanisms (e.g., histone methylation, transcriptional repressor binding). Re-expression of 15-LOX-1 in colon cancer cells can function as an important therapeutic mechanism and could be further exploited to develop novel treatment approaches for this common cancer.

Keywords

15-LOX-1; linoleic acid; apoptosis; colon cancer

1 Introduction

Multiple lines of evidence indicate that diet significantly influences the risk of colon cancer; however, the molecular mechanisms for these dietary effects remain to be defined [1]. In experimental animals, dietary fats vary in their ability to enhance colonic carcinogenesis according to their chemical structure. For example, the position of the first unsaturated function from the methyl terminal group (the n function) is a very important determinant of the effects of polyunsaturated fatty acids (PUFAs) with respect to carcinogenesis. PUFAs with n-6 function, such as linoleic acid and arachidonic acid, promote colonic carcinogenesis, whereas PUFAs with n-3 function, such as Eicosapentaenoic acid and docosahexaenoic acid, protect against colonic carcinogenesis [2]. Although data from epidemiological studies have been inconsistent regarding the relationship between dietary fat intake and the risk of colorectal cancer, the concept that n-6 and n-3 PUFAs have differential effects on tumorigenesis is supported by epidemiological and experimental animal studies [3], including a recently reported prospective study of 73,242 Chinese

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women showing an increased colon cancer risk with increased n-6 PUFA to n-3 PUFA ratio [4].

Lipoxygenases (LOXs), a family of nonheme iron dioxygenases, are named after the specific location in the arachidonic acid carbon chain where the enzyme catalyzes lipid peroxidation (e.g., 15-LOX oxygenates arachidonic acid at the 15th carbon) [5]. Human diets contain manyfold higher levels of linoleic acid than arachidonic acid [6]. Whereas arachidonic acid has multiple oxidative metabolic pathways in humans, linoleic acid metabolism is mainly limited to the 15-LOX-1 pathway, which produces 13-S-HODE [7–9]. Arachidonic acid metabolites, especially PGE2, promote colonic tumorigenesis [10]. In contrast, the role of 15-LOX-1 and 13-S-HODE in tumorigenesis is debated [11,12]. The current article will review and discuss the role of 15-LOX-1 in colonic tumorigenesis on the basis of the currently available literature.

2 Function of 15-LOX-1 in normal cells

2.1 15-LOX-1 and PUFA metabolism

15-LOX-1 is a major contributor to the oxidative metabolism of both n-3 and n-6 PUFAs. 15-LOX-1 oxidative metabolism of n-6 PUFA catalyzes the formation of 13-S-HpODE (precursor of 13-S-HODE) as a major product from linoleic acid and 15-S-HpETE (precursor of 15-S-HETE) as a minor product from arachidonic acid [13]. Additionally, 15-LOX-1 plays a major role in the formation of arachidonic anti-inflammatory products, known as lipoxins [14].

15-LOX-1 enzymatic oxidative metabolism of n-3 PUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), generates potent anti-inflammatory mediators, known as resolvins and protectins, that inhibit inflammation [15]. Resolvins have been divided into 2 classes: the resolvin E (RvE) series (e.g., RvE1), derived from EPA, and the resolvin D (RvD) series (e.g., RvD1), derived from DHA [15]. Protectins [e.g., protectin D1 (PD1)] are another family of DHA derivatives and are distinguished by conjugated triene double-bonds in their structures and neuroprotective effects [15].

The conversion of EPA to RvEs is thought to require the enzymatic activity of LOXs and aspirin-acetylated cyclooxygenase-2 (COX-2); in contrast, the conversion of DHA to RvDs and PDs occurs through LOXs independently of COX-2 [15]. 15-LOX-1 appears to be the most active among the LOXs in forming RvDs and PDs [15]. 15-LOX-1 mediates the conversion of DHA to 17-S-hydroxy-DHA, the precursor for RvDs and PD1, to increase the formation of these potent anti-inflammatory mediators [15–17].

2.2 15-LOX-1 and inflammation control

Proper control of inflammation is essential to human health. Emerging data increasingly support a mechanistic link between chronic inflammation and cancer [18], especially in the case of colonic tumorigenesis [19]. Several lines of evidence support an anti-inflammatory role for 15-LOX-1. 15-LOX-1 overexpression inhibits polymorphonuclear-cell tissue destruction in rabbits [20] and glomerulonephritis in rats [21]. 15-LOX inhibitor PD146176 promotes colitis in mice [22]. Interleukin (IL)-1β is a major proinflammatory cytokine that contribute to the pathogenesis of human colitis [23]. 15-LOX-1 downregulation in human colorectal cancer is associated with IL-1β upregulation, and 15-LOX-1 re-expression in colon cancer cells inhibits IL-1β [6].

Various products of 15-LOX-1 n-3 and n-6 PUFA oxidative metabolism inhibit inflammation. 15-LOX-1 activates peroxisome proliferator-activated receptor (PPAR)-γ through 13-S-HODE [24,25]. PPAR-γ activation inhibits inflammation [26], including

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colitis [27] and colitis-induced promotion of colorectal tumorigenesis [28]. PPAR-γ is being evaluated as a target for the treatment of inflammatory bowel diseases [29]. While 13-S-HODE anti-inflammatory role might be questioned by some [30], 15-LOX-1 inhibits inflammation through various other more extensively studied lipid oxidative metabolites. As mentioned earlier in this article, 15-LOX-1 is critical to the formation of the lipoxins, which promote inflammation resolution [31], and 15-LOX-1 is a major enzyme catalyzing the conversion of n-3 PUFAs to the powerful anti-inflammatory products RvDs and PDs [15–17]. For example, 15-LOX-1 expression in human peripheral mononuclear cells increases formation of PD1, which promotes inflammation resolution by inhibiting leukocyte infiltration and proinflammatory cytokine secretion [32]. In addition, increased production of resolvins and protectins (e.g., RvE1, RvD3, PD1) through 15-LOX-1-mediated metabolism of n-3 PUFAs is associated with suppression of colitis in mice [33].

2.3 15-LOX-1 and terminal differentiation

15-LOX-1 contributes to terminal differentiation of normal cells by promoting maturational degradation of organelles. This role of 15-LOX-1 in organelle degradation during terminal differentiation was first discovered during studies of reticulocyte maturation into red cells [34,35]. Reticulocyte maturation requires cellular organelle degradation, especially degradation of mitochondria [34]. 15-LOX-1 integrates specifically into organelle membranes (e.g., mitochondria membranes) to promote membrane penetration by various degradation enzymes (e.g., proteases) [36,37]. 15-LOX-1 also contributes to the terminal differentiation of cells in the eye lenses [36] and to the mucociliary differentiation of human nasal and bronchial epithelia [38,39].

Loss of the ability to undergo normal cell differentiation is one of the important mechanisms of tumorigenesis [40,41]; cell differentiation, especially terminal cell differentiation, often becomes aberrant in cancer [42,43]. Efforts are being made to develop anticancer therapeutic interventions to restore terminal differentiation in cancer cells [43–46]. Loss of 15-LOX-1 expression, which is common in cancer cells, as discussed later in this review, might promote tumorigenesis by rendering cells unable to undergo terminal differentiation.

3 15-LOX-1 and colon tumorigenesis

3.1 Protumorigenic versus antitumorigenic role of 15-LOX-1

Initially, a protumorigenic role for 15-LOX-1 was proposed on the basis of various observations. First, 13-S-HODE potentiates the mitogenic response to epidermal growth factor in fibroblasts [47], Syrian hamster embryo cells [48], and transformed breast cancer cells (BT-20) [49]. Second, transfection of normal fibroblasts with C-erbB-2 (a proto-oncogene similar to epidermal growth factor) increases 13-S-HODE production [50]. Third, the activity of 13-HODE dehydrogenase, which metabolizes 13-S-HODE to 13-oxooctadecadienoic acid, decreases as colonic epithelial cells undergo malignant transformation [51]; this decrease in 13-HODE dehydrogenase activity was interpreted as a potential mechanism for increasing 13-S-HODE in cancer cells and thus promoting colonic tumorigenesis. This notion was further supported by a report showing that 15-LOX-1 expression was higher in colorectal human tumors than normal undissected tissue samples by Western blotting [52]. However, in the same study, immunohistochemical staining studies of the 15-LOX-1 expression failed to confirm this difference [52]. Furthermore, the same group had shown previously that in contrast to their tissue sample findings, all colon cancer cell lines they tested lack 15-LOX-1 expression and that 15-LOX-1 expression occurs during the induction of differentiation and apoptosis of Caco-2 colon cancer cell line [53,54]. These findings raised questions concerning the concept that 15-LOX-1 has a procarcinogenic role [55].

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Multiple lines of evidence have since confirmed that 15-LOX-1 acts as a tumor suppressor gene. We initially evaluated the hypothesis that 13-S-HODE and 15-LOX-1 are upregulated in colon cancers because of the prior data suggesting a protumorigenic role for 15-LOX-1. We found, however, that 13-S-HODE levels and 15-LOX-1 expression were reduced in human colorectal cancers compared to normal colonic epithelia and that replacing 13-S-HODE in colon cancer cells in vitro inhibited proliferation and induced apoptosis [56]. On the basis of these findings, we proposed the novel concept that 15-LOX-1 plays an antitumorigenic role [56]. Other data reported before our study indirectly supported this concept. First, 13-S-HODE attenuates ornithine decarboxylase activity in rat colons [57] and reverses skin hyperproliferation in guinea pigs [58]. Second, human osteosarcoma cells transfected with human 15-LOX-1 and with enzymatically active expression of 15-LOX-1 grow more than 50% more slowly than do parental cells [8]. Cell growth rates in osteosarcoma cells approach those observed in non-15-LOX-1-expressing clones when 15-LOX-1 expression is lost. Third, the immediate and transient precursor of 13-S-HODE, 13-hydroxyperoxyoctadecadienoic acid, induces apoptosis in human T cells [59]. Fourth, induction of terminal differentiation in transformed Caco-2 colonic cells was associated with 15-LOX-1 expression and 13-S-HODE production in these cells [53]. Subsequent studies by other independent groups further confirmed our initial observation of the downregulation of 15-LOX-1 in colorectal cancer. These studies included follow-up studies from Dr. Eling's group showing that in fresh frozen sections of human colon cancers, 15-LOX-1 expression was downregulated in colon cancer epithelia compared to normal colonic epithelia [60]. Studies by 2 other groups also showed that 15-LOX-1 expression is downregulated in human cancers compared to normal tissues [61,62]. Finally, higher ratios of 15-LOX-1 expression in tumor tissue to 15-LOX-1 expression in normal tissue were associated with better prognosis in patients with stage IV colorectal cancer[62].

3.2 15-LOX-1 expression loss during the multistep process of colonic tumorigenesis

Colon cancer evolves through well-defined clinical stages (e.g., adenoma, invasive cancer) that are associated with the accumulation of various molecular changes [63]. Loss of 15-LOX-1 expression in colonic tumorigenesis occurs at the colorectal-adenoma stage in patients with hereditary familial adenomatous polyposis syndrome [64] and the more commonly occurring sporadic polyps [61,62]. In a study by Yuri et al., the frequency of loss of expression of 15-LOX-1 and the frequency of overexpression of COX-2 increased with increasing stage of progression toward invasive cancer [61], which suggests a shift in the oxidative metabolite profile of PUFA during colonic tumorigenesis from 15-LOX-1 to COX-2.

Because preclinical models suggested a protumorigenic role for 5-LOXs and 12-LOXs in colonic tumorigenesis, we further characterized the metabolic profile of the various LOXs in colorectal adenomas of patients with familial adenomatous polyposis syndrome. The major alterations in the LOX metabolite profile in these adenomas were loss of 15-LOX-1 and decrease in 13-HODE levels compared with levels in nonneoplastic colonic mucosa [65]. A larger study in patients without a history of hereditary colon cancer and with prospective sample collection and assessment of dietary intake of linoleic and arachidonic acids further confirmed that the decrease in 13-HODE production secondary to 15-LOX-1 downregulation occurred early and was the only significant change in LOX metabolic prolife during the transition from normal mucosa to adenoma to colorectal cancer [6].

Representative experimental modeling of loss of 15-LOX-1 expression during human colonic tumorigenesis in animals remains a challenge. Re-expression of 15-LOX-1 in human colorectal cancer cell xenografts inhibits colonic tumorigenesis [66,67]. However, xenograft models of human cancers are limited in their ability to simulate human carcinogenesis. In contrast, transgenic and knockout mouse models are thought to be better models for

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studying the role of specific molecular events in tumorigenesis [68]. However, mice express 12/15-LOX, which can produce either 12-S-HETE, which promotes tumorigenesis, or 13-S-HODE, which inhibits carcinogenesis [69]. Because of this mixed function of the corresponding gene in the mouse, the development of a representative mouse model of 15-LOX-1 loss of expression in colonic tumorigenesis remains a challenge.

3.3 15-LOX-1 and tumor angiogenesis

Angiogenesis is an important mechanism in tumorigenesis [70]. 15-LOX-1 exerted anti-angiogenic effects by inhibiting vascular endothelial growth factor-A and placental growth factor in a rabbit skeletal muscle experimental model [71]. However, the role of 15-LOX-1 in angiogenesis during tumorigenesis remains controversial [12,72]. In one model, 15-LOX-1 re-expression in PC-3 prostatic cancer cells increased vascular epidermal growth factor in vitro and angiogenesis in subcutaneous xenografts [73]. In contrast, several lines of evidence support an anti-angiogenic role for 15-LOX-1, especially through 13-HODE. One study showed that 13-HODE inhibits tumor cell adhesion to endothelial cells, subendothelial matrix, and fibronectin [74]. Decreased 13-HODE levels in endothelial cells were associated with increased tumor cell adhesion to endothelial cells in 5 different human cancer cell lines in vitro [75] and with metastasis formation by syngeneic B10F10 mouse melanoma cells in mice [76]. More recently, targeted 15-LOX-1 expression in mouse endothelial cells via the murine preproendothelin-1 promoter markedly inhibited lung metastasis formation by Lewis lung carcinoma cells and blocked subcutaneous xenograft formation by DA3 mouse mammary adenocarcinoma cells [77]. While information on the role of 15-LOX-1 in tumor angiogenesis in colorectal tumorigenesis models is lacking, the preponderance of evidence from models of tumorigenesis in other organs supports the concept that 15-LOX-1 most likely plays an inhibitory role in tumor angiogenesis.

3.4 15-LOX-1 and colorectal metastasis

The ability of tumors to metastasize is a major determinant of morbidity and mortality of cancer. Metastases develop through a multistep process that involves invasion, migration, and extravasation, among other steps [78]. As reviewed in the prior section, 15-LOX-1 appears to significantly influence the ability of tumor cells to metastasize in various experimental models. 13-HODE levels have been inversely associated with cancer cells ability to attach to endothelial cells and to metastasize in mice [74–76]; transgenic 15-LOX-1 expression in murine endothelial cells inhibits metastasis [77]. Furthermore, 15-LOX-1 re-expression in colon cancer cell lines inhibits their invasiveness, cellular motility, and migration in in vitro models [25,79]. This antimetastatic effect of 15-LOX-1 has been linked to 15-LOX-1 activation of PPAR-γ [25]. 15-LOX-1 activates PPAR-γ in colon cancer cells through 13-S-HODE binding and downregulation of PPAR-δ [80]. PPAR-γ activation inhibits cancer metastasis formation in various experimental tumor models, including colon cancer [81–83], and metastatic cancers have decreased expression of PPAR-γ[84]. Therefore, 15-LOX-1 expression loss in colon cancer cells appears to promote their metastatic potential.

3.5 15-LOX-1 expression loss as a molecular target for tumorigenesis inhibition

To determine whether 15-LOX-1 loss of expression during colonic tumorigenesis can be therapeutically targeted, we examined whether nonsteroidal anti-inflammatory drugs (NSAIDs), putative chemopreventive agents for colon cancer [85], can modulate 15-LOX-1 expression. We found that NSAIDs upregulated 15-LOX-1 expression and increased 13-S-HODE production during apoptosis induction and that these events were critical to NSAIDs ability to induce apoptosis in colorectal cancer cells in vitro [86,87] and in human colorectal cancer cell xenografts in mice [66]. 15-LOX-1 downregulated PPAR-δ, via 13-S-HODE, to induce apoptosis in colorectal cancer cells [66]. Others have also found that NSAIDs,

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including celecoxib, a COX-2 inhibitor, induce 15-LOX-1 during apoptosis in colon cancer cells [62] [88]. NSAIDs restore 15-LOX-1 expression independently of substrate shift by inhibiting COX-2 inhibition [89] through direct modulation of 15-LOX-1 transcriptional regulation [90].

Histone deacetylase inhibitors (HDACIs) are the other class of agents that are known to induce 15-LOX-1 expression in colon cancer cells. HDACIs are a class of promising antitumorigenic agents that are currently under extensive therapeutic development for the treatment of cancer, including colon cancer [91–93]. Various HDACIs, including sodium butyrate, trichostatin A, and HC toxin, induce 15-LOX-1 expression in human colon cancer cell lines [53,54,94–97]. HDACIs are more efficient than NSAIDs in inducing 15-LOX-1 expression in colon cancer cells, especially in the case of depsipeptide, which can induce 15-LOX-1 transcriptional activation at a concentration of approximately 5 nM [95]. However, various colorectal cancer cell lines (e.g., RKO, HCT-116) are resistant to HDACI-induced 15-LOX-1 transcriptional reactivation, and this resistance is highly correlated with lack of impact of HDACIs on survival of cancer cells [95].

White tea extract and Honokiol are other putative antitumorigenic agents that activate 15-LOX-1 to inhibit tumorigenesis [98,99]. 15-LOX-1 is one of various molecular targets for the antitumorigenic effects NSAIDs and HDACIs. The relative significance of 15-LOX-1 to the therapeutic response of NSAIDs and HDACIs in vitro and in vivo has been demonstrated in various experimental models using 15-LOX-1 specific enzymatic activity inhibition, antisense, siRNA knockdown [66,86,87,95,97]. Furthermore, specific 15-LOX-1 re-expression via plasmid or adenoviral delivery system in colon cancer is sufficient to inhibit tumorigenesis in vitro and in vivo independently of drug effects [60,64,80,100].

15-LOX-1 expression induces apoptosis and inhibits tumorigenesis in colon cancer cells via multiple downstream targets (e.g., activation of PPAR-γ; downregulation of PPAR-δ, XIAP, and BCLXL; p53 activation) (Figure 1) [66,80,101,102]. The effects of 15-LOX-1 on PPAR-δ have been linked to direct binding to this downstreatm target by 15-LOX-1 main enzymatic product, 13-S-HODE[66,80]. Interestingly, however, 15-LOX-1 effects on p53 have been shown to be mediated by 15-LOX-1 direct protein-protein interaction to DNA-dependent protein kinase independent of 15-LOX-1 enzymatic activity [103].

4 Mechanisms for 15-LOX-1 transcriptional repression in colon cancer cells

In normal cells, 15-LOX-1 is tightly regulated at the translational level by heterogeneous-nuclear ribonucleoprotein K and heterogeneous-nuclear ribonucleoprotein E1 [104]; however, in cancer cells, 15-LOX-1 is transcriptionally repressed [90,105,106]. Several mechanisms have been identified as contributing to this transcriptional repression on the basis of studies of 15-LOX-1 transcriptional activation in cancer cells by NSAIDs, HDACIs, and cytokines (e.g., IL-4).

4.1 Role of transcriptional factors in 15-LOX-1 transcriptional repression in colon cancer cells

Observations that GATA-6 is downregulated during 15-LOX-1 transcriptional activation by sodium butyrate and NSAIDs suggest that GATA-6 acts a transcriptional repressor by binding to the 15-LOX-1 promoter [90,105]. The potential contribution of GATA-6 to colonic tumorigenesis was further supported by demonstration of GATA-6 overexpression in colorectal cancers [107]. However, specific GATA-6 downregulation (via an siRNA approach) inhibits GATA-6 binding to the 15-LOX-1 promoter but fails to activate 15-LOX-1 transcription [107]. Nevertheless, GATA-6 downregulation in these studies enhanced the ability of HDACIs and NSAIDs to express 15-LOX-1 and induce apoptosis,

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which suggests that other transcriptional regulatory events are involved in the repression of 15-LOX-1 in cancer cells [107].

Another proposed mechanism for the regulation of 15-LOX-1 expression in cancer cells is the binding of activated STAT-6 to the 15-LOX-1 promoter to trigger transcription; this notion is based on data from studies of the effects of IL-4 on 15-LOX-1 transcription in the lung cancer cell line A549 [96]. The contribution of STAT-6 to 15-LOX-1 transcription is questioned, however, because SAHA induces 15-LOX-1 expression in Caco-2 colon cancer cells [97] but also downregulates STAT-6 expression in cutaneous T-cell lymphomas [108]. We found that STAT-6 was not required for 15-LOX-1 transcriptional activation by depsipeptide (a HDACI) in colon cancer cell lines [109].

4.2 Histone remodeling and 15-LOX-1 transcriptional regulation

Various nonspecific HDACIs (e.g., sodium butyrate, SAHA) induce 15-LOX-1 in colon cancer cells [53,54,110]. Depsipeptide, a selective HDAC1 and HDAC2 inhibitor [111], is a more potent than nonspecific HDACIs in inducing 15-LOX-1 transcription to trigger apoptosis [95]. The specificity of HDAC1 and HDAC2effects on 15-LOX-1 repression was further confirmed in studies of HDAC1 and HDAC2 knockdown by siRNA, which showed that these siRNAs, but not knockdown of other HDACs (e.g., HDAC3), activated 15-LOX-1 transcription [95]. HDAC1 and HDAC2 dissociation from the 15-LOX-1 promoter region, which is predicted to recruit a transcription repressor, occurred within 15 minutes during 15-LOX-1 transcriptional activation by depsipeptide [95]. Depsipeptide induces 15-LOX-1 promoter chromatin remodeling (histone 3 [H3] and H4 acetylation). Inhibition of H3 and H4 acetylation in the 15-LOX-1 promoter region by P300 [histone acetyltransferase [112]] knockdown suppressed 15-LOX-1 transcriptional activation by depsipeptide [109]. The ability of depsipeptide to induce chromatin remodeling (H3 acetylation) in the 15-LOX-1 promoter was a predictor of 15-LOX-1 transcriptional activation [109]. These findings indicated that recruitment of HDAC1 and HDAC2 through the NURD complex to the 15-LOX-1 promoter region is an important molecular mechanism for maintaining 15-LOX-1 transcriptional suppression in colon cancer cells and that inhibition of this recruitment, to allow chromatin remodeling in the 15-LOX-1 promoter, is needed to activate 15-LOX-1 transcription.

4.3 Histone methylation and 15-LOX-1 transcriptional regulation in cancer cells

Chromatin structure contributes to transcription regulation [113]. Chromatin is formed by nucleosomes, each consisting of 146 DNA base pairs wrapped around a histone protein octamer composed of double copies of H2A, H2B, H3, and H4 [114]. Histone amino-terminal posttranslational modifications (e.g., acetylation, methylation) modulate chromatin conformation and thus gene transcription [113,115]. Histone acetylation generally facilitates transcriptional activation, whereas other histone modifications, especially histone methylation, have a broader regulatory role that includes both transcription repression and activation [116]. On the basis of our earlier finding that histone acetylation in the 15-LOX-1 promoter was essential for 15-LOX-1 transcriptional activation, we examined whether other histone modifications that can influence histone acetylation as a subsequent eventare involved in 15-LOX-1 transcriptional activation. In a screen of various histone methylation activation and repressor modifications, a histone methylation repressor modification, H3K9me2, was found to be specifically recruited to the 15-LOX-1 promoter in a region where the NURD repression complex is recruited[109]. H3K9me2, a euchromatin transcription-silencing modification [116], is maintained through a dynamic balance between methyltransferases and demethylases [117]. KMT1C (formerly known as G9a) is the primary histone lysine methyltransferase involved in H3K9me2 formation [118–122], and H3K9me2 is demethylated by the histone demethylase KDM3A [117]. H3K9me2

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demethylation via KDM3A recruitment to the 15-LOX-1 promoter is required for 15-LOX-1 transcriptional activation by depsipeptide in Caco-2 colon cancer cells [123]. Thus, histone methylation appears to play an important role in the epigenetic regulation of 15-LOX-1 repression in colon cancer cells.

4.4 15-LOX-1 promoter DNA methylation and 15-LOX-1 transcriptional suppression

The 15-LOX-1 promoter contains CpG islands [124,125] and is methylated in lymphoma, lung, epidermoid, cervical, and prostate cancer cell lines in vitro and in 35% of patients with prostate cancer [126,127]. The demethylation agent 5-aza-2-deoxycytidine (5-aza-dc) reportedly induces 15-LOX-1 expression in colon cancer cell lines [128] and facilitates 15-LOX-1 transcriptional activation by IL-4 or HDACIs in L428 lymphoma cells [125]. In contrast, other reports have indicated that 5-aza-dc failed to induce 15-LOX-1 expression in colon cancer cells [54] and even inhibited 15-LOX-1 gene transcription in prostatic cancer cell lines [126].

We have studied the relationship between 15-LOX-1 promoter DNA methylation and human tumorigenesis in both in vitro and in vivo models of colonic tumorigenesis. We found that the 15-LOX-1 promoter was methylated in colorectal cancer cells in vitro and in 36% (18/50) of colorectal cancer patients but that promoter methylation was virtually absent in the colonic mucosa of 50 subjects with normal colons and no history of colorectal cancer or polyps [129]. 15-LOX-1 promoter DNA methylation levels, however, had no significant correlation with 15-LOX-1 expression levels, and promoter demethylation by DNMT1 and DNMT3b double knockout failed to reestablish 15-LOX-1 expression [129]. These data indicated that 15-LOX-1 promoter methylation was not a primary mechanistic event in 15-LOX-1 transcription suppression in cancer cells.

To assess whether 15-LOX-1 promoter methylation had a secondary role in 15-LOX-1 transcription suppression, we evaluated the mechanisms underlying 5-aza-dc enhancement of 15-LOX-1 transcriptional activation by HDACIs in cancer cells [125]. To see whether these mechanisms were related to DNMT inhibition by 5-aza-dc, we used DNMT1 and DNMT3b knockout models in HCT-116 cells [130]. Our results showed that the synergistic effects of 5-aza-dc and HDACIs are mediated through inhibition of DNMT1 recruitment to the 15-LOX-1 promoter independent of 15-LOX-1 promoter methylation [129]. DNMT1 acts as a co-repressor by recruiting repression complexes containing HDAC1 and HDAC2 to promoters [131–133]. The crucial role of co-regulators (e.g., co-repressors) in gene transcription control in various human diseases, including cancer, is increasingly being recognized [134]. DNMT1 appears to be an important co-repressor of 15-LOX-1 transcription in cancer cells, in light of our finding that DNMT1 binds to the same region in 15-LOX-1 where the HDAC1 and HDAC2 as part of the NURD complex are recruited and that dissociation of DNMT1 from that region, as in the case of the NURD complex, was a predicator of 15-LOX-1 transcriptional activation by HDACIs in colon cancer cells [129]. However, elucidation of the interaction between the NURD complex and DNMT1 in relation to 15-LOX-1 repression requires further studies.

In summary, 15-LOX-1 repression in cancer cells is complex and appears to involve multiple layers of repression mechanisms (Figure 1) that involve GATA-6, DNMT-1, NURD complex, and histone methylation, especially via the H3K9me2 repression modification. Further studies to examine the interplay among these various repression mechanisms are needed.

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5 Role of 15-LOX-1 in other types of cancer in humans

The loss of 15-LOX-1 expression in cancer is not limited to colon cancer but is similarly observed in other major human cancers, including esophageal cancer [135], breast cancer [136], pancreatic cancer [137], urinary blader cancer [138] and lung cancer [139]. While some reports suggest that 15-LOX-1 might have a protumorigenic role in some human cancers, [73,140], data from various experimental models in various human cancers support the concept that 15-LOX-1 plays an important antitumorigenic role, and re-expression of 15-LOX-1 in various cancer cell lines from many other organs besides the colon inhibits tumorigenesis [69,135,141–144].

6 Conclusion

Studies in colon cancer have elucidated the novel concept that loss of 15-LOX-1 contributes to tumorigenesis. Data are accumulating that support the role of 15-LOX-1 as a tumor suppressor, especially in colon cancer, that modulates various antitumorigenic events related to promotion of cell differentiation and apoptosis and inhibition of chronic inflammation, angiogenesis, and metastasis formation. The transcriptional repression of 15-LOX-1 in colon cancer cells is complex and involves multiple mechanisms. Re-expression of 15-LOX-1 in colon cancer cells can function as an important therapeutic mechanism and could be further exploited to develop novel treatment approaches for this common cancer.

Acknowledgments

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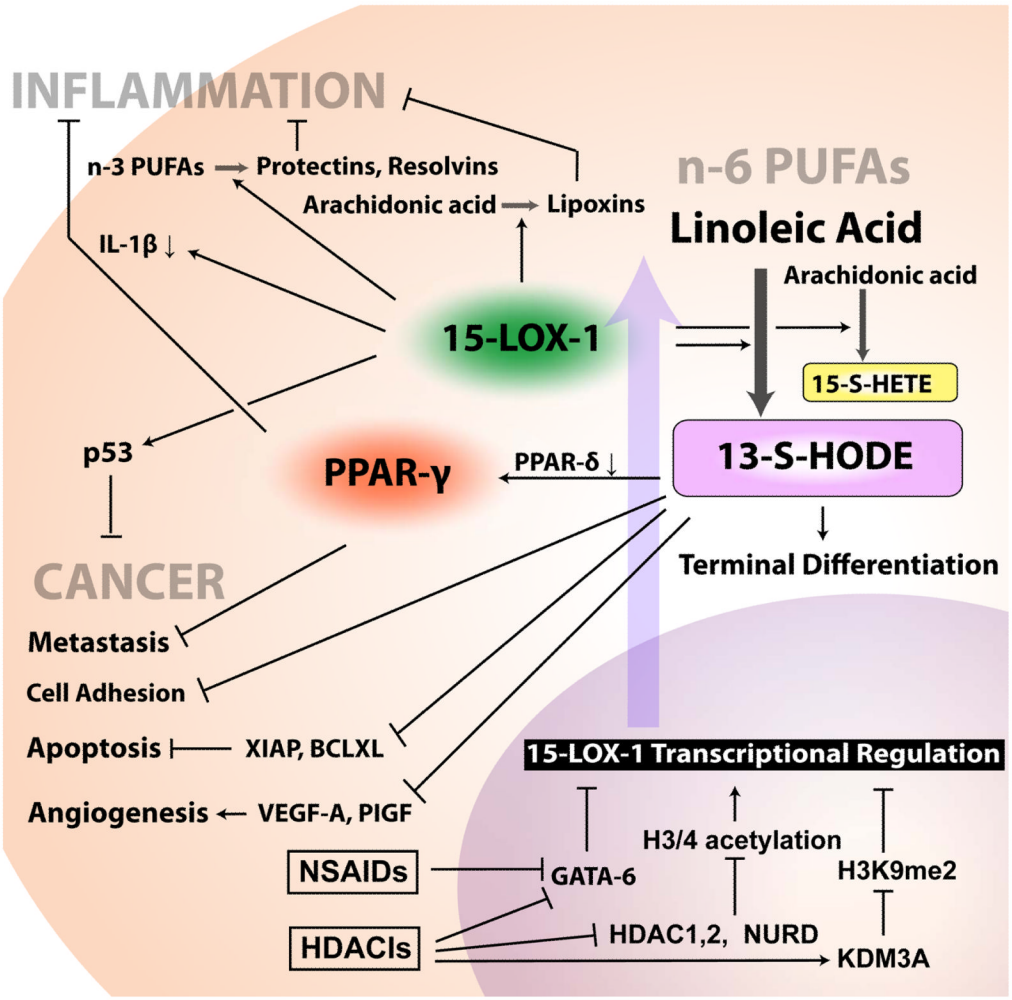

Figure 1.
Proposed model for 15-lipoxygenase-1 (15-LOX-1) transcriptional regulation and its antitumorigenic effects through downstream targets to modulate molecular and cellular events.