Published in final edited form as:

Prostaglandins Other Lipid Mediat. 2013 ; 0: 139–143. doi:10.1016/j.prostaglandins.2012.08.004.

Eicosanoid profiling in colon cancer: emergence of a pattern

Xiangsheng Zuo^a and Imad Shureiqi^a

^aDepartment of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

Abstract

Oxidative metabolism of polyunsaturated fatty acids has been linked to tumorigenesis in general and colonic tumorigenesis in particular. Earlier studies showed that cyclooxygenase-2 (COX-2) and 15-lipoxygenase-1 (15-LOX-1) have opposing impacts on colonic tumorigenesis: COX-2 promotes while 15-LOX-1 inhibits colonic tumorigenesis. Advances in liquid chromatography/mass spectrometry have allowed for measurement of various products of oxidative metabolism in a single colonic biopsy specimen. Studies of LOX products in preclinical models and in patients with familial adenomatous polyposis and sporadic colorectal tumorigenesis indicate that LOX pathways are shifted during colonic tumorigenesis and that the main shift is downregulation of 15-LOX-1. This shift occurs during the polyp formation stage and thus offers the opportunity to modulate tumorigenesis early by correcting 15-LOX-1 downregulation.

Keywords

Eicosanoid profiling; lipoxygenases; cyclooxygenases; 15-LOX-1; colon cancer

1. Introduction

Colon cancer remains a leading cause of cancer deaths in the United States (1). An improved understanding of critical mechanisms of colonic tumorigenesis could provide much-needed theoretical knowledge to facilitate development of better treatment and prevention strategies for this disease. Because the most common site for cancer in the alimentary tract is the colon (1), diet has long been investigated for its potential role in colonic tumorigenesis. Dietary fats in particular have received significant attention as potentially being linked to colonic tumorigenesis because western diets that are rich in fats are associated with high risk of colon cancer (2).

In experimental animal studies, not all dietary fats are equal in their contribution to colonic tumorigenesis. Polyunsaturated fatty acids (PUFAs) have stronger effects on colonic carcinogenesis than do saturated fatty acids (3, 4). Furthermore, the position of the first unsaturated function from the methyl terminal group (the n function) is a very important determinant of PUFAs' effects on colonic carcinogenesis. PUFAs with n-6 function, such as linoleic acid and arachidonic acid, promote carcinogenesis, while PUFAs with n-3 function,

© 2012 Elsevier Inc. All rights reserved.

Correspondence to: Imad Shureiqi, MD, Department of Gastrointestinal Medical Oncology, Unit 426, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4009. Phone: (713) 792-2828. Fax: (713) 745-1163. (ishureiqi@mdanderson.org).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

such as fish oil, lack carcinogenic effects or inhibit carcinogenesis in the same animal models (5). Consumption of red meat, a rich source of n-6 PUFAs, increases the risk of colon cancer more than the consumption of fish, which is a rich source of n-3 PUFAs, as shown in a large epidemiological study (6). Oxidative metabolism of n-6 PUFAs is considered to be necessary for n-6 PUFAs to promote colonic carcinogenesis. This notion is based on studies showing that n-6 PUFAs increase early colonic cell proliferation events only in their oxidized derivative forms (7).

It is widely known that oxidative metabolism of arachidonic acid by cyclooxygenases (COXs) generates prostaglandins, one of which, prostaglandin E2 (PGE2), contributes to colonic tumorigenesis (8). However, the link between PUFA oxidative metabolism and colonic tumorigenesis is complex and also involves other enzymes, such as members of the lipoxygenase (LOX) family, which in humans includes 5-LOX, 12-*S*-LOX, 15-LOX-1, and 15-LOX-2 (9).

While the majority of studies to date that have examined the role of oxidative metabolism of n-6 PUFAs have been mainly focused on a single pathway, advances in liquid chromatography/mass spectrometry (LC/MS/MS) detection technology now allow for comprehensive simultaneous assessment of multiple pathways in small biological samples, such as biopsy specimens (10–12). Such a comprehensive approach allows a better assessment of the overall balance in metabolic alterations during tumorigenesis. The current article aims to provide a picture of the emerging pattern of alterations in n-6 PUFA oxidative metabolism in colonic tumorigenesis.

2. COX-2, 15-LOX-1, and colonic tumorigenesis

2.1. COX-2, prostaglandin E2, and colonic tumorigenesis

PGE2 is an oxidative product of metabolism of arachidonic acid by COXs. PGE2 promotes tumorigenesis through multiple cellular mechanisms, including promotion of cell proliferation and angiogenesis and suppression of apoptosis (13). In vivo, PGE2 enhances intestinal tumor formation in Apc^{Min} mice (14), whereas genetic deletion of the EP-1, EP-2, and EP-4 PGE2 receptors inhibits colonic tumorigenesis (15–17). In humans, PGE2 levels are higher in colon cancers than in normal colonic mucosa (13); high PGE2 urine levels are associated with increased risk of colon cancer (18). The increase in PGE2 production during colorectal tumorigenesis is considered to be mediated by overexpression of COX-2, which is common in human colorectal cancer and adenoma and promotes colorectal tumorigenesis (19).

2.2. 15-LOX-1, 13-HODE, and colonic tumorigenesis

15-LOX-1 is an inducible and highly regulated enzyme in normal human cells (20) that plays a key role in the production of lipid signaling mediators—e.g., 13-*S*-hydroxyoctadecadienoic acid (13-*S*-HODE) from linoleic acid (21). 15-LOX-1 is important to the resolution of inflammation (22) and to terminal differentiation of normal cells (20). 15-LOX-1 expression loss is pervasive in human cancer cells (23). 15-LOX-1 is downregulated in various major human cancers, including cancers of the colon (24–26), breast (27), lung (23, 28), and pancreas (29). Some reports have proposed a protumorigenic role for 15-LOX-1 based on studies in prostate and breast cancer models (30, 31). However, a number of lines of evidence support the concept that 15-LOX-1 is an important tumor suppressor gene (32). First, 15-LOX-1 re-expression significantly contributes to the antitumorigenic effects of nonsteroidal antiinflammatory drugs and histone deacetylase inhibitors in colorectal and other cancer cells (11, 26, 33–38). Second, a specific role of 15-LOX-1 in inhibiting tumorigenesis is supported by findings that 15-LOX-1 re-expression in human colon cancer cells by either plasmid or adenoviral vectors induces apoptosis in vitro

(11, 39, 40) and inhibits xenograft formation in vivo (25, 39). Third, more recently, we have reported that targeted transgenic 15-LOX-1 expression in the intestine suppresses azoxymethane-induced colonic tumorigenesis (41), which further support a tumor suppressive role for 15-LOX-1, especially in colonic tumorigenesis (42).

13-HODE inhibits proliferation and induces apoptosis in cancer cells (9, 24, 34, 43) through peroxisome proliferator-activated receptor- γ activation (40). Other data also link 13-HODE to tumorigenesis inhibition: 13-HODE attenuates ornithine decarboxylase activity in rat colons (44), reverses skin hyperproliferation in guinea pigs (45), and induces apoptosis in leukemia cells in vitro (46). Studies of skin tumorigenesis in a transgenic mouse model of epidermis-type 12-*S*-LOX indicated that 13-HODE production is associated with antitumorigenic effects (47). Furthermore, in a mouse-skin tumorigenesis model (48) in which linoleic acid is not converted into arachidonic acid but is converted into 13-HODE, linoleic acid inhibits rather than promotes carcinogenesis (49). Thus, 13-HODE has antitumorigenic effects, in contrast to arachidonic acid metabolites such as PGE₂.

2.3. 15-LOX-1 and COX-2 have opposite expression patterns during colonic tumorigenesis

Caco-2 colon cancer cells represent an in vitro model for terminal cell differentiation: treatment of Caco-2 cells with various stimuli, such as sodium butyrate, produces Caco-2 cells that have metabolic and ultrastructure features closely resembling those of normal colonic epithelium (50). Induction of terminal differentiation in Caco-2 cells is associated with 15-LOX-1 re-expression and COX-2 downregulation (51). This inverse correlation between 15-LOX-1 and COX-2 expression is not unique to Caco-2 cells; it has also been observed in other in vitro systems, such as during differentiation of human tracheobronchial epithelial cells (52). More importantly, this inverse correlation between 15-LOX-1 and COX-2 expression has been demonstrated in humans during the progressive steps of colonic tumorigenesis (53). Studies in other human cancers, such as breast cancer, have also shown an inverse correlation between 15-LOX-1 and COX-2 expression (54).

This inverse correlation between 15-LOX-1 and COX-2 expression is mechanistically important to the development of tumorigenesis: 15-LOX-1 conditional expression in virally transformed human embryonic kidney cells inhibits anchorage-independent growth, while COX-2 expression via the same systems increases anchorage-independent growth (55). Sulforaphane, a vegetable isothiocyanate, upregulates 15-LOX-1 and downregulates COX-2 expression when inhibiting intestinal polyp formation in APC^{Min} mice (56). Similarly, Honokiol, a natural product of *Magnolia officinalis* with antitumorigenic activity, upregulates 15-LOX-1 and downregulates COX-2 expression when inhibiting gastric tumorigenesis (57).

15-LOX-1 inhibits interleukin-1 β and tumor necrosis factor- α , which are signaling activators of nuclear factor- κ B (NF- κ B) (58, 59) during colonic tumorigenesis (12, 41). Expression of 15-LOX-1 in colon cancer cells in vitro and in murine intestine during azoxymethane-induced colonic tumorigenesis in vivo represses NF- κ B activation (41, 60). NF- κ B activation induces COX-2 expression (58, 59). We therefore propose that 15-LOX-1 inhibition of COX-2 expression via NF- κ B suppression is a potential mechanism for the inverse association between 15-LOX-1 and COX-2 expression during colonic tumorigenesis (Figure 1).

3. LOX profiling in human colonic tumorigenesis

The LOX family include several members, which are named after the position on the arachidonic acid carbon chain where they exert their enzymatic activities (61). 5-LOX, 12-*S*-LOX, 15-LOX-1, and 15-LOX-2 are expressed in humans (61). Studies of eicosanoid

profiling were limited to examination of a single pathway until advances in LC/MS/MS permitted examination of multiple pathways in tissue samples (10). Using this new methodology, it was demonstrated that endogenous levels of PGE₂ were increased while levels of 13-HODE were concomitantly decreased during 7,12-dimethylbenz[a]anthracene-induced oral tumorigenesis in hamsters (10). These findings supported the inverse relationship between 15-LOX-1 and COX-2 expression during tumorigenesis. The LOX profile during tumorigenesis, however, remained undefined.

LOX profiling in colonic tumorigenesis made possible by advances in LC/MS/MS has consistently demonstrated a similar pattern in preclinical and clinical studies. In the first study of LOX profiling during Caco-2 cell differentiation, we observed 15-LOX-1 upregulation and increased 13-S-HODE production as the only significant changes during terminal cell differentiation; we observed no significant changes in the 5-LOX, 12-S-LOX, and 15-LOX-2 pathways (11). Human studies confirmed that this pattern is relevant clinically. We first found that in patients with familial adenomatous polyposis, the expression of 15-LOX-1 was reduced in colonic polyps compared to paired normal tissue, while the expression of other LOXs was unchanged. In agreement with these findings, LC/MS/MS analyses of normal and colorectal polyp samples from patients with familial adenomatous polyposis showed that 13-HODE levels were reduced in polyps while the products of the other LOX pathways were not significantly altered (11).

We later conducted a prospective study (53) in which we collected colonic tissue samples from subjects with normal colon and no history of colorectal cancer or polyps (n = 49), subjects with colorectal polyps but not colorectal cancer (n = 36), and subjects with colorectal cancer (n = 40). The study was limited to patients without known familial adenomatous polyposis and without a significant family history of cancer, and thus the patients in the study truly represented patients with sporadic colorectal tumorigenesis. The prospective design of the study allowed for the collection of important data used to adjust for various medication and dietary confounders that could influence the activity of the LOX pathways (e.g., intake of nonsteroidal antiinflammatory drugs, calcium, and arachidonic and linoleic acid). No significant differences were found between the groups with regard to these confounders (12). However, linoleic acid intake was approximately 10 times arachidonic acid intake, which confirmed the predominance of linoleic acid as the primary n-6 PUFA in the human diet (12). The only significant alteration in LOX pathway products in the sporadic colorectal polyps and cancers compared to the normal colon mucosa was decrease in the level of 13-HODE (12). This finding confirmed the central and early role of 15-LOX-1 downregulation in alteration of LOX metabolism during colonic tumorigenesis. This role has been mechanistically supported in studies of targeted intestinal 15-LOX-1 expression in mice showing the ability of 15-LOX-1 expression to suppress colonic tumorigenesis (41).

4. Conclusion

Preclinical studies and studies in humans of hereditary and nonhereditary colorectal tumorigenesis demonstrate that the specific pattern of LOX oxidative product formation during colorectal tumorigenesis is primarily characterized by downregulation of 15-LOX-1 expression and reduction of 13-HODE production. This downregulation of 15-LOX-1 expression is counterbalanced by upregulation of COX-2 expression and increased PGE₂ production. This emerging pattern of the shift in n-6 PUFA oxidative metabolism during colonic tumorigenesis could inform efforts directed at colon cancer chemoprevention.

Acknowledgments

This work was partially supported by the National Cancer Institute through grant R01-CA137213 to I.S. The University of Texas MD Anderson Cancer Center is supported in part by the National Institutes of Health through Cancer Center Support Grant CA016672.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012 Jan-Feb;62(1):10–29. Epub 2012/01/13. eng. [PubMed: 22237781]
2. Kushi L, Giovannucci E. Dietary fat and cancer. *The American Journal of Medicine*. 2002; 113(9, Supplement 2):63–70.
3. Nigro ND, Singh DV, Campbell RL, Sook M. Effect of dietary beef fat on intestinal tumor formation by azoxymethane in rats. *J Natl Cancer Inst*. 1975; 54(2):439–42. [PubMed: 1113326]
4. Broitman SA, Vitale JJ, Vavrousek-Jakuba E, Gottlieb LS. Polyunsaturated fat, cholesterol and large bowel tumorigenesis. *Cancer*. 1977; 40(5 Suppl):2455–63. [PubMed: 303539]
5. Chapkin RS, McMurray DN, Lupton JR. Colon cancer, fatty acids and anti-inflammatory compounds. *Curr Opin Gastroenterol*. 2007 Jan; 23(1):48–54. [PubMed: 17133085]
6. Willett W, Stampfer M, Colditz G, Rosner B, Speizer F. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med*. 1990; 323(24):1664–72. [PubMed: 2172820]
7. Bull AW, Nigro ND, Golembieski WA, Crissman JD, Marnett LJ. In vivo stimulation of DNA synthesis and induction of ornithine decarboxylase in rat colon by fatty acid hydroperoxides, autoxidation products of unsaturated fatty acids. *Cancer Res*. 1984 Nov; 44(11):4924–8. [PubMed: 6488154]
8. Backlund MG, Mann JR, DuBois RN. Mechanisms for the Prevention of Gastrointestinal Cancer: The Role of Prostaglandin E₂. *Oncology*. 2005; 69(Suppl 1):28–32. [PubMed: 16210874]
9. Shureiqi I, Lippman SM. Lipoyxygenase modulation to reverse carcinogenesis. *Cancer Res*. 2001 Sep 1; 61(17):6307–12. [PubMed: 11522616]
10. Yang P, Chan D, Felix E, Madden T, Klein RD, Shureiqi I, et al. Determination of endogenous tissue inflammation profiles by LC/MS/MS: COX- and LOX-derived bioactive lipids. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2006; 75(6):385–95.
11. Shureiqi I, Wu Y, Chen D, Yang XL, Guan B, Morris JS, et al. The Critical Role of 15-Lipoxygenase-1 in Colorectal Epithelial Cell Terminal Differentiation and Tumorigenesis. *Cancer Res*. 2005 Dec 15; 65(24):11486–92. [PubMed: 16357157]
12. Shureiqi I, Chen D, Day RS, Zuo X, Hochman FL, Ross WA, et al. Profiling lipoxygenase metabolism in specific steps of colorectal tumorigenesis. *Cancer Prev Res (Phila)*. 2010 Jul; 3(7):829–38. [PubMed: 20570882]
13. Backlund MG, Mann JR, Dubois RN. Mechanisms for the prevention of gastrointestinal cancer: the role of prostaglandin E₂. *Oncology*. 2005; 69(Suppl 1):28–32. [PubMed: 16210874]
14. Wang D, Wang H, Shi Q, Katkuri S, Walhi W, Desvergne B, et al. Prostaglandin E₂ promotes colorectal adenoma growth via transactivation of the nuclear peroxisome proliferator-activated receptor δ . *Cancer Cell*. 2004; 6(3):285–95. [PubMed: 15380519]
15. Watanabe K, Kawamori T, Nakatsugi S, Ohta T, Ohuchida S, Yamamoto H, et al. Role of the prostaglandin E receptor subtype EP1 in colon carcinogenesis. *Cancer Res*. 1999 Oct 15; 59(20):5093–6. [PubMed: 10537280]
16. Sonoshita M, Takaku K, Sasaki N, Sugimoto Y, Ushikubi F, Narumiya S, et al. Acceleration of intestinal polyposis through prostaglandin receptor EP2 in Apc(Delta 716) knockout mice. *Nat Med*. 2001 Sep; 7(9):1048–51. [PubMed: 11533709]
17. Mutoh M, Watanabe K, Kitamura T, Shoji Y, Takahashi M, Kawamori T, et al. Involvement of prostaglandin E receptor subtype EP(4) in colon carcinogenesis. *Cancer Res*. 2002 Jan 1; 62(1):28–32. [PubMed: 11782353]

18. Murff HJ, Shu X-O, Li H, Dai Q, Kallianpur A, Yang G, et al. A Prospective Study of Dietary Polyunsaturated Fatty Acids and Colorectal Cancer Risk in Chinese Women. *Cancer Epidemiology Biomarkers & Prevention*. 2009 Aug; 18(8):2283–91.
19. Wang D, DuBois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. *Oncogene*. 2009; 29(6):781–8. [PubMed: 19946329]
20. Kuhn H, Walther M, Kuban RJ. Mammalian arachidonate 15-lipoxygenases structure, function, and biological implications. *Prostaglandins Other Lipid Mediat*. 2002 Aug; 68–69:263–90.
21. Brash AR, Boeglin WE, Chang MS. Discovery of a second 15S-lipoxygenase in humans. *Proc Natl Acad Sci U S A*. 1997; 94(12):6148–52. [PubMed: 9177185]
22. Serhan CN. Resolution Phase of Inflammation: Novel Endogenous Anti-Inflammatory and Proresolving Lipid Mediators and Pathways. *Annu Rev Immunol*. 2007; 25(1):101–37. [PubMed: 17090225]
23. Moussalli MJ, Wu Y, Zuo X, Yang XL, Wistuba, Raso MG, et al. Mechanistic contribution of ubiquitous 15-lipoxygenase-1 expression loss in cancer cells to terminal cell differentiation evasion. *Cancer Prev Res (Phila)*. 2011 Dec; 4(12):1961–72. [PubMed: 21881028]
24. Shureiqi I, Wojno KJ, Poore JA, Reddy RG, Moussalli MJ, Spindler SA, et al. Decreased 13-S-hydroxyoctadecadienoic acid levels and 15-lipoxygenase-1 expression in human colon cancers. *Carcinogenesis*. 1999 Oct; 20(10):1985–95. [PubMed: 10506115]
25. Nixon JB, Kim KS, Lamb PW, Bottone FG, Eling TE. 15-Lipoxygenase-1 has anti-tumorigenic effects in colorectal cancer. *Prostaglandins Leukot Essent Fatty Acids*. 2004 Jan; 70(1):7–15. [PubMed: 14643174]
26. Heslin MJ, Hawkins A, Boedefeld W, Arnoletti JP, Frolov A, Soong R, et al. Tumor-associated down-regulation of 15-lipoxygenase-1 is reversed by celecoxib in colorectal cancer. *Ann Surg*. 2005 Jun; 241(6):941–6. discussion 6–7. [PubMed: 15912043]
27. Jiang WG, Watkins G, Douglas-Jones A, Mansel RE. Reduction of isoforms of 15-lipoxygenase (15-LOX)-1 and 15-LOX-2 in human breast cancer. *Prostaglandins, Leukotrienes and Essential Fatty Acids*. 2006 Apr; 74(4):235–45.
28. Yuan H, Li M-Y, Ma LT, Hsin MKY, Mok TSK, Underwood MJ, et al. 15-Lipoxygenases and its metabolites 15(S)-HETE and 13(S)-HODE in the development of non-small cell lung cancer. *Thorax*. 2010 Apr 1; 65(4):321–6. [PubMed: 20388757]
29. Hennig R, Kehl T, Noor S, Ding XZ, Rao SM, Bergmann F, et al. 15-Lipoxygenase-1 Production is Lost in Pancreatic Cancer and Overexpression of the Gene Inhibits Tumor Cell Growth. *Neoplasia*. 2007 Nov; 9(11):917–26. [PubMed: 18030360]
30. Kelavkar UP, Nixon JB, Cohen C, Dillehay D, Eling TE, Badr KF. Overexpression of 15-lipoxygenase-1 in PC-3 human prostate cancer cells increases tumorigenesis. *Carcinogenesis*. 2001 Nov; 22(11):1765–73. [PubMed: 11698337]
31. Kerjaschki D, Bago-Horvath Z, Rudas M, Sexl V, Schnecklenleithner C, Wolbank S, et al. Lipoxygenase mediates invasion of intrametastatic lymphatic vessels and propagates lymph node metastasis of human mammary carcinoma xenografts in mouse. *The Journal of Clinical Investigation*. 2011; 121(5):2000–12. [PubMed: 21540548]
32. Il Lee S, Zuo X, Shureiqi I. 15-Lipoxygenase-1 as a tumor suppressor gene in colon cancer: is the verdict in? *Cancer Metastasis Rev*. 2011; 30(3):481–91. [PubMed: 22037943]
33. Shureiqi I, Chen D, Lee JJ, Yang P, Newman RA, Brenner DE, et al. 15-LOX-1: a novel molecular target of nonsteroidal anti-inflammatory drug-induced apoptosis in colorectal cancer cells. *J Natl Cancer Inst*. 2000 Jul 19; 92(14):1136–42. [PubMed: 10904086]
34. Shureiqi I, Xu X, Chen D, Lotan R, Morris JS, Fischer SM, et al. Nonsteroidal anti-inflammatory drugs induce apoptosis in esophageal cancer cells by restoring 15-lipoxygenase-1 expression. *Cancer Res*. 2001 Jun 15; 61(12):4879–84. [PubMed: 11406566]
35. Shureiqi I, Jiang W, Zuo X, Wu Y, Stimmel JB, Leesnitzer LM, et al. The 15-lipoxygenase-1 product 13-S-hydroxyoctadecadienoic acid down-regulates PPAR-delta to induce apoptosis in colorectal cancer cells. *Proc Natl Acad Sci U S A*. 2003 Aug 19; 100(17):9968–73. [PubMed: 12909723]

36. Wu J, Xia HH, Tu SP, Fan DM, Lin MC, Kung HF, et al. 15-Lipoxygenase-1 mediates cyclooxygenase-2 inhibitor-induced apoptosis in gastric cancer. *Carcinogenesis*. 2003 Feb; 24(2): 243–7. [PubMed: 12584173]
37. Hsi LC, Xi X, Lotan R, Shureiqi I, Lippman SM. The histone deacetylase inhibitor suberoylanilide hydroxamic acid induces apoptosis via induction of 15-lipoxygenase-1 in colorectal cancer cells. *Cancer Res*. 2004 Dec 1; 64(23):8778–81. [PubMed: 15574791]
38. Deguchi A, Xing SW, Shureiqi I, Yang P, Newman RA, Lippman SM, et al. Activation of protein kinase G up-regulates expression of 15-lipoxygenase-1 in human colon cancer cells. *Cancer Res*. 2005 Sep 15; 65(18):8442–7. [PubMed: 16166323]
39. Wu Y, Fang B, Yang XQ, Wang L, Chen D, Krasnykh V, et al. Therapeutic Molecular Targeting of 15-Lipoxygenase-1 in Colon Cancer. *Mol Ther*. 2008; 16(5):886–92. [PubMed: 18388920]
40. Zuo X, Wu Y, Morris JS, Stimmel JB, Leesnitzer LM, Fischer SM, et al. Oxidative metabolism of linoleic acid modulates PPAR-beta/delta suppression of PPAR-gamma activity. *Oncogene*. 2006 Feb 23; 25(8):1225–41. [PubMed: 16288226]
41. Zuo X, Peng Z, Wu Y, Moussalli MJ, Yang XL, Wang Y, et al. Effects of Gut-Targeted 15-LOX-1 Transgene Expression on Colonic Tumorigenesis in Mice. *J Natl Cancer Inst*. 2012 May 2; 104(9): 709–16. [PubMed: 22472308]
42. Umar A. Is 15-LOX-1 a Tumor Suppressor? *J Natl Cancer Inst*. 2012 May 2; 104(9):645–7. [PubMed: 22472307]
43. Shureiqi I, Chen D, Lotan R, Yang P, Newman RA, Fischer SM, et al. 15-Lipoxygenase-1 mediates nonsteroidal anti-inflammatory drug-induced apoptosis independently of cyclooxygenase-2 in colon cancer cells. *Cancer Res*. 2000 Dec 15; 60(24):6846–50. [PubMed: 11156377]
44. Bull AW, Earls SM, Blackburn ML. Regulation of the induction of ornithine decarboxylase in short-term rat colon organ culture by dexamethasone and 13-hydroxyoctadecadienoic acid (13-HODE). *Life Sci*. 1993; 53:337–85.
45. Miller CC, Ziboh VA. Induction of epidermal hyperproliferation by topical n-3 polyunsaturated fatty acids on guinea pig skin linked to decrease levels of 13-hydroxyoctadecadienoic acid (13-HODE). *J Invest Dermatol*. 1990; 94:354–8.
46. Jostardt K, Gellert N, Rubic T, Weber C, Kuhn H, Johansen B, et al. Dissociation of apoptosis induction and CD36 upregulation by enzymatically modified low-density lipoprotein in monocytic cells. *Biochem Biophys Res Commun*. 2002 Jan 25; 290(3):988–93. [PubMed: 11798172]
47. Muller K, Siebert M, Heidt M, Marks F, Krieg P, Furstenberger G. Modulation of Epidermal Tumor Development Caused by Targeted Overexpression of Epidermis-type 12S-Lipoxygenase. *Cancer Res*. 2002 Aug 15; 62(16):4610–6. [PubMed: 12183416]
48. Leyton J, Lee ML, Locniskar M, Belury MA, Slaga TJ, Bechtel D, et al. Effects of type of dietary fat on phorbol ester-elicited tumor promotion and other events in mouse skin. *Cancer Res*. 1991; 51(3):907–15. [PubMed: 1899048]
49. Fischer SM, Hagerman RA, Li-Stiles E, Lo HH, Maldve RE, Belury MA, et al. Arachidonate has protumor-promoting action that is inhibited by linoleate in mouse skin carcinogenesis. *J Nutr*. 1996; 126(4 Suppl):1099S–104S. [PubMed: 8642440]
50. Pinto M, Robine-Leon S, Appay M, Kedinger M, Triadou N, Dussaulx E, et al. Enterocyte-like differentiation and polarization of the human colon carcinoma cell line Caco-2 in culture. *Biol Cell*. 1983; 47:323–30.
51. Kamitani H, Geller M, Eling T. Expression of 15-lipoxygenase by human colorectal carcinoma Caco-2 cells during apoptosis and cell differentiation. *J Biol Chem*. 1998 Aug 21; 273(34):21569–77. [PubMed: 9705287]
52. Hill EM, Eling T, Nettekheim P. Changes in expression of 15-lipoxygenase and prostaglandin-H synthase during differentiation of human tracheobronchial epithelial cells. *Am J Respir Cell Mol Biol*. 1998 May; 18(5):662–9. [PubMed: 9569236]
53. Yuri M, Sasahira T, Nakai K, Ishimaru S, Ohmori H, Kuniyasu H. Reversal of expression of 15-lipoxygenase-1 to cyclooxygenase-2 is associated with development of colonic cancer. *Histopathology*. 2007; 51(4):520–7. [PubMed: 17711445]

54. Jiang WG, Douglas-Jones A, Mansel RE. Levels of expression of lipoxygenases and cyclooxygenase-2 in human breast cancer. *Prostaglandins Leukot Essent Fatty Acids*. 2003 Oct; 69(4):275–81. [PubMed: 12907138]
55. Yu MK, Moos PJ, Cassidy P, Wade M, Fitzpatrick FA. Conditional expression of 15-lipoxygenase-1 inhibits the selenoenzyme thioredoxin reductase: modulation of selenoproteins by lipoxygenase enzymes. *J Biol Chem*. 2004 Jul 2; 279(27):28028–35. [PubMed: 15123685]
56. Khor TO, Hu R, Shen G, Jeong W-S, Hebbar V, Chen C, et al. Pharmacogenomics of cancer chemopreventive isothiocyanate compound sulforaphane in the intestinal polyps of ApcMin/+ mice. *Biopharm Drug Dispos*. 2006; 27(9):407–20. [PubMed: 16952200]
57. Liu SH, Shen CC, Yi YC, Tsai JJ, Wang CC, Chueh JT, et al. Honokiol inhibits gastric tumorigenesis by activation of 15-lipoxygenase-1 and consequent inhibition of peroxisome proliferator-activated receptor- γ and COX-2-dependent signals. *Br J Pharmacol*. 2010; 160(8): 1963–72. [PubMed: 20649594]
58. Sethi G, Shanmugam MK, Ramachandran L, Kumar AP, Tergaonkar V. Multifaceted link between cancer and inflammation. *Biosci Rep*. 2012 Feb; 32(1):1–15. [PubMed: 21981137]
59. Oshima H, Oshima M. The inflammatory network in the gastrointestinal tumor microenvironment: lessons from mouse models. *J Gastroenterol*. 2012 Feb; 47(2):97–106. [PubMed: 22218775]
60. Cimen I, Astarci E, Banerjee S. 15-lipoxygenase-1 exerts its tumor suppressive role by inhibiting nuclear factor-kappa B via activation of PPAR gamma. *J Cell Biochem*. 2011; 112(9):2490–501. [PubMed: 21544861]
61. Brash AR. Lipoxygenases: occurrence, functions, catalysis, and acquisition of substrate. *J Biol Chem*. 1999; 274(34):23679–82. [PubMed: 10446122]

Highlights

- N-6 PUFA oxidative metabolism via cyclooxygenases and lipoxygenases modulates colorectal tumorigenesis
- COX-2 is upregulated and 15-LOX-1 is downregulated during colorectal tumorigenesis
- 15-LOX-1 downregulation is the primary lipoxygenase shift during colorectal tumorigenesis

Figure 1.

Schematic representation of proposed theoretical model for the mechanism of the inverse association between 15-LOX-1 and COX-2 expression during colonic tumorigenesis. 15-LOX-1 downregulates IL-1 β and TNF- α expression which represses NF- κ B activation to subsequently inhibit COX-2 transcription and its tumorigenesis promotion.