Is 15-LOX-1 a Tumor Suppressor?
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A number of enzymes in the cyclooxygenase and lipoxygenase pathways process fatty acids to generate a variety of bioactive lipids. Recent findings that link inflammation to carcinogenesis have started to reveal how these bioactive lipids function in cellular signaling pathways as lipid messengers that mediate responses to cellular injury through inflammatory processes (1). Downstream effects of these bioactive lipids are determined by tissue-specific isomerases and specific receptors present in different organs. Two main pathways lead to the generation of bioactive lipids, which differ markedly in their biological activities. The cyclooxygenases lead mostly to the generation of prostaglandins and thromboxanes, whereas the lipoxygenases lead to the formation of leukotrienes and lipoxins among other products (Figure 1). Collectively, these signaling 20-carbon fatty acids are termed eicosanoids. They act by autocrine and paracrine mechanisms to regulate the dynamics of inflammation, immunity, and smooth muscle contraction and as messengers in the central nervous system (1, 2). It is not surprising that many of these bioactive molecules play a critical role in inflammation, but their opposing functions are often underappreciated.

The role of inflammation in carcinogenesis is well established and has been summarized by Wang and Dubois (1); however, important questions remain. It is still not clear which specific component(s) or which phase(s) of the inflammatory process are involved in carcinogenesis or at which stage of carcinogenesis the primary effects of inflammation occur. Furthermore, the key question of whether inflammation alone is sufficient and necessary to promote carcinogenesis in

**Figure 1.** Roles of bioactive lipids in cell signaling and cancer. A) Generation of bioactive lipids by the lipoxygenase and cyclooxygenase pathways. Membrane phospholipids including arachidonic acid and linoleic acid are converted by a series of enzymes in the lipoxygenase and cyclooxygenase pathways into bioactive lipids that include prostaglandins (PGs), prostacyclins, thromboxanes (TXs), leukotrienes (LTs), lipoxins, hydroxyeicosatetraenoic acids (HETEs), and hydroxyoctadecadienoic acids (HODEs). B) Opposing roles of these bioactive lipids in several key processes. These include regulation of inflammation, proliferation, and apoptosis, leading to a pro-carcinogenic or an anticarcinogenic effect.
some settings is still unanswered. If so, a strategy that reverses inflammation might be used to prevent and treat some types of cancer.

Unsaturated fatty acids and metabolites of arachidonic and linoleic acids form bioactive lipids that function in the initiation, maintenance, and resolution of inflammation. Colorectal epithelium may be especially susceptible to the effects of bioactive lipids because of its direct proximity to their dietary sources. Lipoxigenases are lipid-peroxidizing enzymes that catalyze the dioxygenation of polyunsaturated fatty acids. More work is needed to fully understand the complex nature of these bioactive lipids in diverse biologic processes, but more and more evidence is emerging that suggests that lipoxigenases have many important roles in human diseases including cancer.

Two different 15-lipoxigenase enzymes, 15-LOX-1 and 15-LOX-2, are found in humans, with distinct expression patterns throughout the body. The functions of the 15-LOX-1 enzyme and its products, 15-S-hydroxyeicosatetraenoic acid (15-S-HETE) and 13-S-hydroxyoctadecadienoic acid (13-S-HODE), are diverse; reportedly, they are chemoattractants for neutrophils (3), inhibit the production of superoxide by macrophages, affect the expression of adhesion molecules (4), and inhibit nuclear factor-κB (NF-κB), whereas they activate peroxisome proliferator-activated receptor-γ (PPAR-γ) (5). Expression of 15-LOX-1 in cancer cell lines has led to apoptosis. Other data show that celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, is able to stimulate 15-LOX-1 expression in a COX-2-independent manner (6). However, the role of 15-LOX-1 in carcinogenesis remains controversial in the published literature (7,8). It is possible that the different expression patterns of the different 15-LOX enzymes have opposing effects on the downstream lipid mediators (eg, 15-HETE and 13-HODE) in different tissues during tumorigenesis.

In this issue of the Journal, Zuo et al. (9) provide further evidence for the role of 15-LOX-1 as a tumor suppressor in colorectal cancer. To delineate the role of 15-LOX-1 in carcinogenesis, Zuo et al. humanized mice for the ALOX15 gene in the background of its mouse ortholog, 12/15-LOX. Although arachidonic acid is converted to 12-S-HETE in mice, it is converted to 15-S-HETE, which would be likely to have very different functions (10). The authors engineered 15-LOX-1 transgenic mice that expressed 15-LOX-1 under the control of the villin promoter, which resulted in mostly gastrointestinal and renal tubular tissue-specific expression. Upon exposure to azoxymethane, a strong carcinogen, the mice expressing 15-LOX-1 showed statistically significantly fewer colorectal tumors than exposed wild-type mice, and the number of tumors was inversely related to the gene dosage. Mice that were heterozygous for the 15-LOX-1 transgene, from two independent lineages, showed an approximately 40%–57% reduction in the number of colorectal tumors, whereas homozygous mice, which had greater expression of the transgene, showed an even larger reduction in tumor number (approximately 56%–70%). These results clearly suggest a tumor suppressor function of 15-LOX-1 in colorectal cancers.

To investigate the mechanism of this tumor suppressive effect, Zuo et al. (9) showed elevated levels of tumor necrosis factor alpha (TNF-α) and inducible nitric oxide synthase (iNOS) in azoxymethane-induced colon tumors of both wild-type and 15-LOX-1 mice were less elevated in the presence of 15-LOX-1, which suggested that 15-LOX-1-mediated inhibition of TNF-α-iNOS signaling may suppress colonic tumorigenesis. TNF-α activates NF-κB as well as iNOS, which is a downstream target for NF-κB in carcinogenesis. Expression of 15-LOX-1 reduced the expression of mRNA for Toll-like receptors 1 and 2 and NF-κB, which function mainly in the reduction or resolution of inflammation. Previous data have been inconsistent with regard to the effects of 12/15-LOX on this pathway, showing that it both inhibits and activates TNF-α-iNOS signaling in mouse models (7,8). Again, previous results might be discordant because TNF-α expression is increased by 12-HETE, the product of 12/15-LOX, but inhibited by 13-HODE, the product of 15-LOX-1 (7,8). The current results of Zou et al. (9) clearly show that 15-LOX-1 suppresses TNF-α and iNOS expression as a mechanism to inhibit colonic tumorigenesis. Furthermore, 15-LOX-1 overexpression in normal colonic mucosa appears to directly inhibit IL-1α/β, TNF-α, TLR1/2, iNOS, and NF-κB expression. This is intriguing because it seems to be a multipronged inhibition of the expression of a cascade of molecules that are critical to the inflammatory process, which suggests that 15-LOX-1 plays a pivotal role in the resolution phase of inflammation.

The data from preclinical studies that have been used to understand the function of human 15-LOX-1 have heretofore been mixed and confusing, probably because of species–specific variations in orthologous enzymes and their varying levels of expression in different organs of different species. For example, recent data have shown that not only are the products of the mouse ortholog 12/15-LOX different from those of the human enzymes but also their expression profiles in the different tissues vary. These experiments, which use 15-LOX-1 transgenic mice to determine a direct effect of human 15-LOX-1 on colorectal tumorigenesis, shed new light on their action. However, it is still possible that transgenic expression of human 15-LOX-1 in mouse epithelial cells may not be an ideal model for colorectal tumorigenesis because of differences in species. Also, targeting of transgenic 15-LOX-1 expression to epithelial intestinal cells provides no information on the contribution of its expression in stromal cells to colorectal tumorigenesis. Future studies that target 15-LOX-1 expression in stromal cells will be required. In addition, there may be events upstream of 15-LOX-1 activity that help to regulate colorectal carcinogenesis because its natural promoter is tightly regulated (11). Although these data are intriguing, additional work will eventually be needed on modulation of targeted 15-LOX-1 expression via direct or indirect interventions to clarify the role of the lipoxigenase pathway and to better understand the specific role of 15-LOX-1 in carcinogenesis.

References


**Notes**

The author claims no conflict of interest.

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