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Review

Eicosanoid profiling in colon cancer: Emergence of a pattern

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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.

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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, 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

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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-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-gamma 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-1β and tumor necrosis factor-α, which are signaling activators of nuclear factor-κβ (NF-κβ) [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-κβ activation [41,60]. NF-κβ activation induces COX-2 expression [58,59]. We therefore propose that 15-LOX-1 inhibition of COX-2 expression via NF-κβ suppression is a potential mechanism for the inverse association between 15-LOX-1 and COX-2 expression during colonic tumorigenesis (Fig. 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