Colon cancer, fatty acids and anti-inflammatory compounds

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Purpose of review

To outline recent findings on the efficacy of *n*-3 polyunsaturated fatty acids in the prevention/treatment of inflammatory bowel disease and colorectal cancer.

Recent findings

Compelling data indicate a functional link between chronic inflammation and colon cancer. With respect to environmental risk factors, there is growing evidence that long-chain *n*-3 polyunsaturated fatty acids found in fish oil suppress inflammatory bowel diseases and colon cancer risk in humans. Unfortunately, the molecular basis of the effect of *n*-3 polyunsaturated fatty acids on inflammation/colitis-associated colon cancer risk is still largely obscure. In this review, we focus on recent studies which address three emerging mechanisms of *n*-3 polyunsaturated fatty acids action: (1) metabolic interconversion into bioactive eicosanoids, (2) modulation of nuclear receptor activation, and (3) alteration of membrane phospholipid composition and functionality of lipid microdomains.

Summary

The consumption of dietary fish oil may prove to be an effective adjuvant therapy in colon cancer. Therefore, it is both appropriate and timely to determine precisely how *n*-3 polyunsaturated fatty acids modulate cell signaling networks, and reduce the risk of developing colon cancer and inflammatory disorders of the intestine.

Keywords

chemoprotection, colon cancer, docosahexaenoic acid, eicosapentaenoic acid, fish oil, inflammatory bowel disease

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Abbreviations

COX	cyclooxygenase
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
IBD	inflammatory bowel disease
PG	prostaglandin
PPAR	peroxisome proliferator-activated receptor
PUFA	polyunsaturated fatty acid

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Introduction

Colorectal cancer continues to pose a serious health problem in the US. Over a lifetime, a person has a 1 : 18 chance of developing invasive colorectal cancer. In addition, inflammatory bowel disease (IBD) patients are at high risk for developing colon cancer [1]. Colorectal cancer evolves from a multistep process and is a disease strongly influenced by diet. Among dietary factors, there is growing epidemiological, clinical and experimental evidence which suggests a protective effect of *n*-3 polyunsaturated fatty acids (PUFAs; found in fish oil) on colon cancer [2–11]. Eicosapentaenoic acid (EPA; $20:5^{\Delta 5,8,11,14,17}$) and docosahexaenoic acid (DHA, $22:6^{\Delta 4,7,10,13,16,19}$) are typical *n*-3 PUFAs, defined according to the position of the first double bond from the methyl end of the molecule which is designated '*n*-3'. In contrast, dietary lipids rich in *n*-6 PUFAs (found in vegetable oils), e.g. linoleic acid ($18:2^{\Delta 9,12}$) and arachidonic acid ($20:4^{\Delta 5,8,11,14}$), enhance the development of colon tumors [2,3,12,13]. These effects are exerted at both the initiation and postinitiation stages of carcinogenesis [6,10,12,14]. Consistent with human clinical trials [7,8,11,15], experimental studies have shown that the balance between colonic epithelial cell proliferation and apoptosis can be favorably modulated by dietary *n*-3 PUFAs, conferring resistance to toxic carcinogenic agents [10,16,17]. This is significant because the typical Western diet contains 10–20 times more *n*-6 than *n*-3 PUFAs [18]. Unfortunately, to date, a unifying mechanistic hypothesis addressing how *n*-3 PUFAs selectively suppress colon cancer compared to *n*-6 PUFAs is lacking.

Link between chronic inflammation and colon cancer

Human IBDs are chronic, relapsing inflammatory conditions of unknown etiology. Genetic, immunological and environmental factors have been implicated [1,19]. These diseases are characterized by two overlapping clinical phenotypes, i.e. ulcerative colitis and Crohn's

disease. Ulcerative colitis primarily involves the colon with inflammation restricted to the mucosa. The inflammation in Crohn's disease often involves the small intestine along with the colon and other organs [20]. Crohn's disease affects more than 500 000 individuals in the US and represents the second most common chronic inflammatory disorder after rheumatoid arthritis. In addition, the risk of developing colorectal cancer increases around 0.5–1% each year after 7 years in patients with chronic intestinal inflammation [1]. Despite compelling data indicating a functional link between inflammation and colon cancer, however, the pathways regulating initiation and maintenance of inflammation during cancer development remain poorly understood. From a dietary perspective, a growing number of published reports support the contention that bioactive food components containing *n*-3 PUFAs modulate important determinants which link inflammation to cancer development and progression [21–25]. Therefore, it is important to identify overlapping regulatory relationships among genes considered to drive inflammation-associated colonic tumor development.

Putative mechanisms of action

The long-chain *n*-3 PUFAs present in dietary fish oil, EPA and DHA, affect diverse physiological processes including cell membrane structure/function, eicosanoid signaling, nuclear receptor activation, and whole-body glucose and lipid metabolism, thereby providing significant protection against a variety of apparently unrelated human diseases [26–29]. *n*-3 PUFAs are rapidly incorporated into cells, primarily into membrane phospholipids at the *sn-2* position [30,31], and, in general, the cellular level is readily influenced by diet [32,33]. The presence of long-chain *n*-3 PUFAs in membrane phospholipids imparts unique physicochemical properties to cellular membranes, and DHA-induced alterations in membrane structure and function have been proposed to underlie its pleiotropic salutary effects [34,35,36••,37]. The following sections describe three mechanistic models which accommodate diverse views on *n*-3 PUFAs effects in the colon.

Metabolism hypothesis: prostaglandin metabolism

Arachidonic acid is the primary precursor for prostaglandins (PGs), hydroxy fatty acids, sulfidopeptide-leukotrienes and lipoxins, collectively referred to as eicosanoids. These oxygenated metabolites are formed rapidly upon stimulus and, acting as autacoids, exert a profound influence on many cellular reactions. Specifically in relation to pathology of the colon, enzymes directly catalyzing the synthesis and degradation of PGE_2 are overexpressed and downregulated in colorectal cancer and IBD, respectively [38,39]. This is significant because recent evidence indicates that cyclooxygenase (COX)-2-derived PGE_2 can promote tumor initiation and progression by enhancing cell proliferation, angiogenesis, cell migration and invasion, while inhibiting apoptosis [40–43]. With respect to dietary fatty acids, it is well documented that EPA and DHA supplant *n*-6 PUFAs, including linoleic acid and arachidonic acid (the major eicosanoid precursor), and can therefore dramatically alter both the spectrum and biological properties of COX and lipoxygenase metabolites produced by cells located in the intestinal mucosa (Fig. 1) [15,44,45••]. For example, in contrast to arachidonic acid-derived PGE_2, EPA-derived PGE_3 exhibits antiproliferative/chemoprotective properties [46,47].

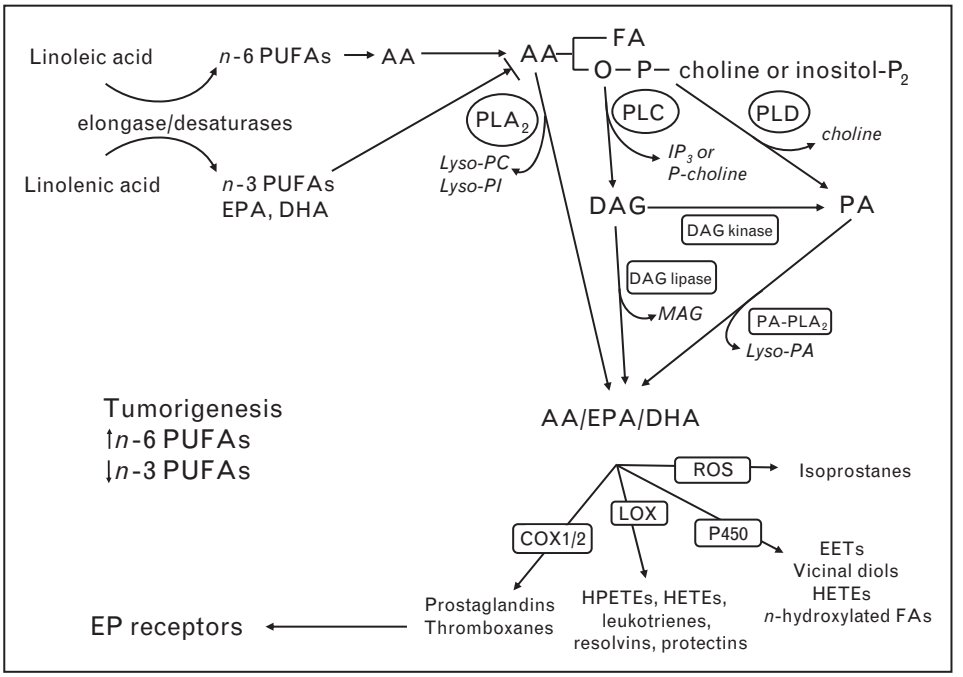
With regard to intestinal inflammatory diseases, it is important to recognize the fact that lamina propria mononuclear cells produce high levels of PGE_2, which acts in part via the PG receptor EP4 as an immunomodulator in maintaining mucosal homeostasis [48–50]. This may explain why medications which dually inhibit COX-1 and -2 are associated with escalating intestinal inflammatory activity [51,52]. Since EPA and DHA inhibit COX-1 [45••,53], it is possible that *n*-3 PUFAs can act to both promote and inhibit inflammation, depending on the inflammatory stimulus, the predominant prostanoid produced, and the profile of prostanoid receptor expression.

Lipoxygenase metabolism

With respect to the 5-lipoxygenase metabolic pathway, it has long been appreciated that EPA is comparable to arachidonic acid as a substrate, and produces less-potent inflammatory mediators [54]. This is noteworthy, because 5-lipoxygenase signaling pathways appear to be intrinsically linked with oncogenic signals involved in epithelial cell survival, apoptosis, and neutrophil infiltration [55,56]. Diets rich in *n*-3 PUFAs are also capable of influencing *in vivo* levels of 13-hydroxyoctadecadienoic acid [57]. This is significant because 13-hydroxyoctadecadienoic acid, a 15-lipoxygenase-1 metabolite of linoleic acid, is capable of inhibiting colon cancer development [58]. Curiously, 13-hydroxyoctadecadienoic acid may play a promoting role in the development of prostate cancer [59]. Lipoxins (lipoxin A_4 and 15-epi-lipoxin A_4) derived from the dual oxygenation of arachidonic acid via both 15- and 5-lipoxygenase enzymes, have been shown to play a role in the resolution of mucosal inflammation [60]. Recent data support the hypothesis that IBD may be caused, in part, by defective lipoxin biosynthesis [61]. Results from several laboratories indicate that a number of cell types are capable of generating novel lipoxin products, i.e. resolvins and protectins, from EPA and DHA [62,63]. Collectively, these findings may form the basis for some of the beneficial actions of EPA in the management of IBD [63,64••]. Future studies are needed in order to determine whether these metabolites are produced naturally, in the absence of aspirin.

Figure 1 *n*-3 PUFAs antagonize arachidonic acid metabolism, reducing the production of proinflammatory eicosanoids and colon cancer risk

AA, arachidonic acid (20 : 4*n*-6); COX, cyclooxygenases; DAG, diacylglycerol; DHA, docosahexaenoic acid (22 : 6*n*-3); EETs, epoxide fatty acyl intermediates; EP, prostaglandin E receptors; EPA, eicosapentaenoic acid (20 : 5*n*-3); FA, fatty acid; HETEs, hydroxyeicosatetraenoic fatty acids; HPETEs, hydroperoxyeicosatetraenoic fatty acids; IP_3, inositol 1,4,5-trisphosphate; LOX, lipoxygenases; LysoPA, lysophosphatidic acid; LysoPC, lysophosphatidylcholine; LysoPI, lysophosphatidylinositol; PA, phosphatidic acid; PLA_2, phospholipase A_2; PLC, phospholipase C; PLD, phospholipase D; P450, cytochrome P450 metabolic pathways; ROS, reactive oxygen species.



Unesterified fatty acids

A number of investigators have hypothesized that intracellular 'free' unesterified arachidonic acid promotes apoptosis in colonocytes [65–68]. This is significant because decreased colonocyte and T cell apoptosis is believed to directly contribute to the development of colon cancer and IBD, respectively [17,19,69]. What is not clear is how intracellular long-chain *n*-3 PUFAs influence this putative pathway. One would expect that since dietary EPA and DHA reduce membrane phospholipid arachidonic levels [35,70], endogenous unesterified arachidonic acid levels would decrease, resulting in a reduction of apoptosis. In fact, the opposite appears to be the case, i.e. EPA and DHA promote apoptosis in colonocytes and T cells [10,71].

Interactive effect of n-3 polyunsaturated fatty acids and butyrate

A very exciting and unexpected outcome of our studies was the demonstration that the protective effect of *n*-3 PUFAs with respect to colon tumor development was enhanced when a highly fermentable fiber, pectin, rather than a poorly fermentable fiber, cellulose, was added to the diet [10]. This chemopreventive effect was mediated in part by the upregulation of targeted apoptosis of DNA adducts during tumor initiation [14,72] and spontaneous apoptosis during promotion [17]. With respect to a mechanism of action, pectin is metabolized by bacteria within the lumen of the gut to butyrate and other short-chain fatty acids. We have recently shown that the ability of pectin/butyrate to promote apoptosis in colonocytes is enhanced by feeding/coculturing with DHA [14,73,74]. These data indicate that highly fermentable fiber, which generates butyrate in the colon, only has chemotherapeutic value when *n*-3 PUFAs is the lipid source. This critical observation emphasizes the need to examine both the lipid and fiber composition of diets. The failure to address an interaction between fat and fiber may explain why the chemoprotective effects of *n*-3 PUFAs may be obscured in prospective cohort studies [75].

Nuclear receptor hypothesis

Recent data indicate that ligands for peroxisome proliferator-activated receptors (PPARs) α, δ and γ inhibit IBD and colon carcinogenesis [76,77,78•]. Interestingly, PPARγ agonists antagonize inflammatory responses by transrepression of NF-κB target genes [79]. With respect to ligand-binding specificity, however, this class of nuclear receptor binds *n*-3 and *n*-6 PUFAs with equal affinity and lacks fatty acid class (*n*-3 vs. *n*-6) specificity [80–83]. Therefore, the anti-inflammatory/chemoprotective effects of *n*-3 PUFAs are likely not mediated directly via PPARs.

The regulation of the stereotypical proinflammatory transcription factor NF-κB is critically important in terms of linking IBD and colon cancer [84–86,87•]. NF-κB appears to be a double-edged sword capable of influencing both mucosal inflammation and repair, with the stimulatory environment largely determining whether

its effect is protective or deleterious for the host [88,89]. EPA, DHA and, perhaps, their bioactive metabolites are capable of suppressing NF-κB (Fig. 2) [70,90,91]. Importantly, in contrast, arachidonic acid can activate NF-κB in certain model systems [92,93], consistent with its well-documented proinflammatory/carcinogenic properties [13]. Interestingly, Hwang *et al.* [94,95] have reported that DHA may be a pan-inhibitor for various Toll-like receptors, capable of suppressing NF-κB activation induced by various Toll-like receptor agonists. These data provide a putative link between *n*-3 PUFAs, NF-κB, innate immunity and IBD. Additional studies are needed in order to determine if these observations can be validated *in vivo*.

Membrane hypothesis

Intestinal immune homeostasis and the control of damaging inflammation to the mucosa is regulated in part by the crosstalk between T cells, dendritic antigen-presenting cells in the lamina propria and epithelial cells [96•]. In all cases the plasma membranes from these cell types contain specific detergent-resistant domains in which key signal transduction proteins are localized. These regions are classified as 'lipid rafts', and are composed mostly of cholesterol and sphingolipids, and therefore do not integrate well into the fluid phospholipid bilayers causing them to form microdomains [97]. Generally, activation of T cells by antigen-presenting cells *in vivo* depends on the formation of an immunological synapse. During immunological synapse formation, rafts compartmentalize the activated receptor, e.g. T cell receptors and associated signaling molecules, thus providing an environment conducive to signal transduction. Although the role of the immunological synapse with regard to T cell activation has been challenged recently, there is overwhelming evidence that lipid raft integrity is a prerequisite for optimized T cell receptor signal transduction and immune response [98,99]. With respect to the diverse biological effects of *n*-3 PUFAs, increasing evidence suggests that DHA is a unique fatty acid because it significantly alters basic properties of cell membranes, including acyl chain order and fluidity, phase behavior, elastic compressibility, ion permeability, fusion, rapid flip-flop, and resident protein function [31,37,100]. As a result of its polyunsaturation, DHA and, possibly, EPA are sterically incompatible with sphingolipid and cholesterol, and thus may alter lipid raft behavior and protein function (Fig. 3) [101]. Since dietary *n*-3 PUFAs are incorporated into colonocyte, T cell and antigen-presenting cell membranes [54,70,72], we hypothesized that PUFA classes (*n*-6 vs. *n*-3) would differentially modulate cell membrane microdomains. Overall, our findings provide compelling evidence demonstrating that dietary sources of *n*-3 PUFAs can profoundly alter the biochemical makeup of T cell lipid rafts and colonocyte caveolae membrane microdomains, thereby influencing

Figure 2 Modulation of nuclear transcription factor activation by dietary polyunsaturated fatty acids

ER, endoplasmic reticulum; FABP, fatty acid binding proteins (molecular chaperone); PPAR, peroxisome proliferator-activated receptors; PUFA, polyunsaturated fatty acids; RXR, retinoid X receptors.

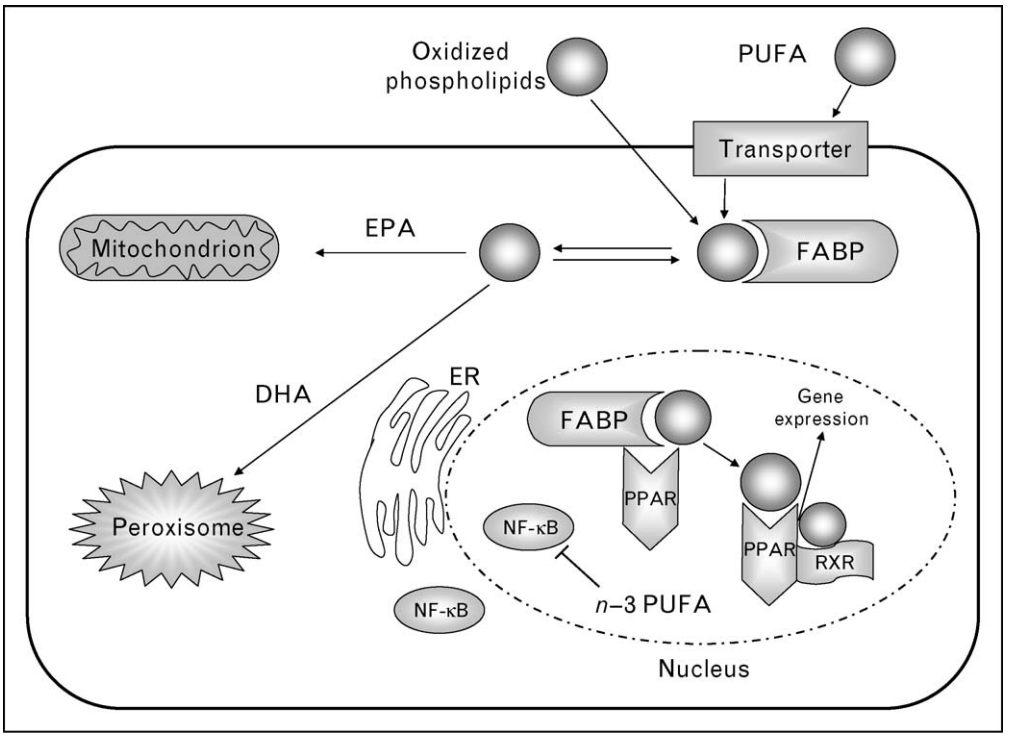
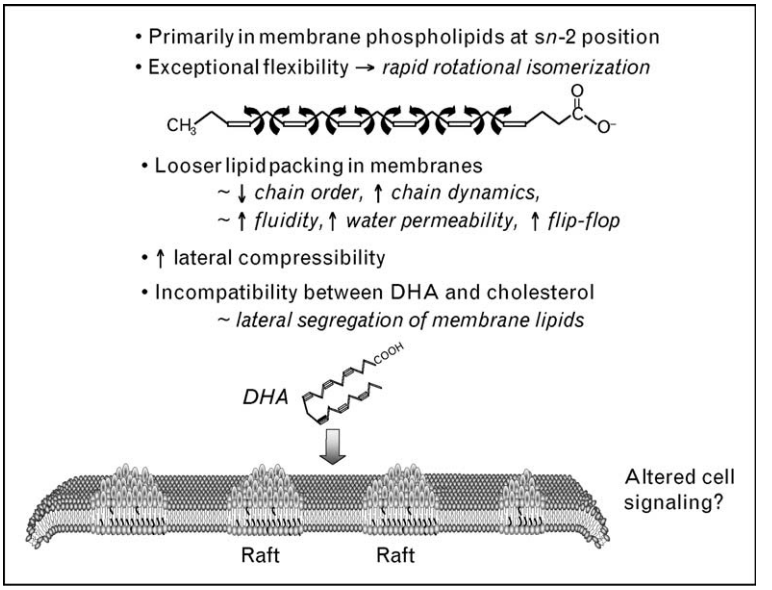


Figure 3 Membrane-altering properties of docosahexaenoic acid

Dietary lipids are incorporated into cell membranes and alter cholesterol/sphingolipid-rich plasma membrane microdomains (i.e. rafts/caveolae) in T cells and colonocytes. This can alter the dynamic partitioning of transduction proteins required for cell proliferation, apoptosis and differentiation.



cellular signaling, protein trafficking and immune cell function [34,35,36••,70]. Consistent with these in-vivo observations, there is some evidence that PUFAs, in general, block dendritic cell activation by interfering with the formation of the immunological synapse [102•,103]. The fatty acid specificity and relevance of these observations need, however, to be evaluated in feeding trials.

Conclusion

A growing body of literature supports the contention that bioactive food components containing EPA and DHA are important in suppressing IBD and colon cancer. Although the mechanism of EPA and DHA action is still not fully defined in molecular terms, it is becoming increasingly clear that these fatty acids are pleiotropic. The challenge for the future is to determine precisely how *n*-3 PUFAs alter membrane microdomain structure and function, eicosanoid metabolism, nuclear receptor activation, and the formation of reactive oxygen products.

In the last few years there has been overwhelming evidence supporting a role for nonsteroidal anti-inflammatory drugs in reducing colon cancer risk and colorectal adenomas [104]. Due to the of side-effects associated with these drugs [105], however, patients with IBD are counseled currently to avoid conventional nonsteroidal anti-inflammatory drugs and to proceed cautiously with the use of COX-2 inhibitors. We propose that dietary *n*-3 PUFAs are ideally suited to work either without drugs, or synergistically with drugs resulting in lower dosage while offering widespread benefits.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 90–94).

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