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Diet and gut microbes act coordinately to enhance programmed cell death and reduce colorectal cancer risk

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Abstract

Diet is an important risk factor for colorectal cancer (CRC) and several dietary constituents implicated in CRC are modified by gut microbial metabolism. Microbial fermentation of dietary fiber produces short chain fatty acids, e.g., acetate, propionate, and butyrate. Dietary fiber has been shown to reduce colon tumors in animal models and, *in vitro*, butyrate influences cellular pathways important to cancer risk. Furthermore, work from our group suggests that the combined effects of butyrate and omega-3 polyunsaturated fatty acids (n-3 PUFA) may enhance the chemopreventive potential of these dietary constituents. We postulate that the relatively low intakes of n-3 PUFA and fiber in Western populations and the failure to address interactions between these dietary components may explain why chemoprotective effects of n-3 PUFA and fermentable fibers have not been detected consistently in prospective cohort studies. In this review, we summarize the evidence outlining the effects of n-3 long-chain PUFA and highly fermentable fiber with respect to alterations in critical pathways important to CRC prevention, particularly intrinsic mitochondrial-mediated programmed cell death resulting from the accumulation of lipid reactive oxygen species (ferroptosis), and epigenetic programming related to lipid catabolism and beta-oxidation associated genes.

Keywords

n-3 PUFA; fermentable fiber; ferroptosis; diet interaction; colon cancer

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Introduction

CRC is the third most common cancer in the U.S. [1], CRC and precursor lesions (e.g., hyperplastic and adenomatous polyps) [2], could be greatly reduced through dietary modification (i.e., increased dietary fiber intake and altered fat intake) [3]. In the 2018 Colorectal Cancer Report, part of the WCRF/AICR Continuous Update Project, the Expert Panel classified evidence supporting consumption of fiber-rich foods and CRC protection as 'convincing' [4], noting a 9% decrease in risk for every 10 g/d increase in fiber among 15 studies in the meta-analysis. Inconsistencies across epidemiologic studies are attributed in part to lower and narrower ranges of fiber intake in Western populations [5]. Intakes greater than the current recommendations (28 g/d for women/35 g/d for men) show robust CRC protection (RRs 0.72 to 0.90) [2,6–8]. However, less than 5% of Americans meet recommended intakes for dietary fiber (mean ~15 g/d) [2,9]. One hypothesized chemoprotective mechanism is fiber fermentation to short-chain fatty acids (SCFA), particularly butyrate, by gut microbiota [10–12]. Given the importance of fiber fermentation, consideration of fiber subtypes and variation in microbial capacity to produce butyrate [13], are important. We review evidence that fiber type in concert with other dietary factors modulates the relation between dietary fiber and CRC risk.

Several mechanisms have been hypothesized to explain how dietary fiber may reduce CRC, including a reduction in secondary bile acids, reduced intestinal transit time, and increased stool bulk [10–12]. One hypothesized chemoprotective mechanism is fiber fermentation to short-chain fatty acids (SCFA), particularly butyrate, by gut microbiota [10–12]. Butyrate is a potent histone deacetylase inhibitor[14,15] associated with reduced CRC risk [14,16–18]. Thus, dietary factors that may influence the production of butyrate are important to understand. Indeed, it is becoming increasingly apparent that modulation and consideration of fiber subtypes (i.e., soluble and insoluble or more and less fermentable) can influence the microbial interspecies competition to alter butyrate production [13,19–21]. However, given the importance of fiber fermentation as a source for butyrate, very few studies in humans have looked at fiber subtype and results have included both null [8,22,23] and inverse associations [24–27] with CRC. We hypothesize that the inconsistencies may be due in part to the interaction of other dietary factors with fiber. Therefore, in this review, we discuss evidence that fiber type in concert with other dietary factors (i.e., n-3 PUFA) modulates the relation between dietary fiber and CRC risk.

In observational studies, evidence is mixed for associations between subtypes of fat and CRC [8,28]. Omega 3 (n-3; α-linolenic acid, ALA) and omega 6 (n-6; α-linoleic acid, LA) PUFA are essential nutrients that are incorporated into tissue membranes, and have a variety of physiologic roles. Long-chain n-3 PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish oils [29], can be produced from ALA, but the process is inefficient in humans, and there is competition with synthesis of other n-6 PUFA, which are found in much greater abundance in a typical Western diet [30]. While both are structural components and substrates of eicosanoid-related pathways, in general, PUFA derived from n-6 are pro-inflammatory whereas those produced from n-3 tend to have opposing effects [31,32]. Given the strong association between inflammation and CRC [32], higher intakes of n-3 PUFA provide biological plausibility for a chemoprotective effect [33].

As with dietary fiber, preclinical models consistently show reduced CRC risk with n-3 PUFA [34–37]. However, epidemiologic data are less consistent in part because intakes are often low and most studies do not adequately capture supplemental fish oil intake. Two meta-analyses concluded that fish intake is associated with decreased CRC risk [38,39]; however, two systematic reviews of n-3 PUFA on cancer risk qualitatively concluded that there is inadequate [40] or limited [41] evidence to suggest an association. A recent publication reported no overall association between n-3 PUFA and CRC risk among 123,529 individuals; however, in sub-site analyses, n-3 PUFA intakes were positively associated with distal colon cancer, but inversely associated with risk of rectal cancer in men [42]. Conversely, separate evaluation in the same cohort suggests that n-3 PUFA intake after CRC diagnosis may have a protective effect on survival [43]. Compared with women who consumed <0.1 g/d of marine n-3 PUFA, those who consumed >0.3 g/d had a reduced CRC-specific mortality (HR: 0.59, 95% CI: 0.35, 1.01), and those who increased their intake by at least 0.15 g/d after diagnosis had an even greater reduction (HR: 0.3; 95% CI: 0.14, 0.64, *P-trend* <0.001). In the VITamins And Lifestyle (VITAL) cohort (n=68,109), evaluating fish oil supplement use—where doses are often much higher than what can be obtained from diet—users on 4+ d/wk for 3+yr experienced 49% lower CRC risk than nonusers (HR = 0.51, 95% CI = 0.26–1.00; P trend = 0.06) [44]. Interestingly, CRC patients who consumed dark fish (>1/wk) after diagnosis had longer disease-free survival [45] , supporting further the need for higher doses than typically obtained with a US diet.

Interaction of Long-Chain n-3 PUFA and Dietary Fiber in Clinical Studies

Fat and fiber are two dietary components with the greatest impact on tumor development, and data support the concept that the type of fat or fiber is actually more important to tumor development than total amounts of either component [9,46–50]. Unfortunately, the effect of combinations of specific subtypes of dietary fiber and fatty acids and risk of CRC in humans is just beginning to be evaluated. This is an important consideration given their varied biologic, biochemical, and metabolic roles [8,9,48,51]. Among the nearly 97,000 Seventh Day Adventists, risk of CRC was reduced by 22% among all vegetarians combined compared to non-vegetarians, but the protection was greatest among pescovegetarians, who consumed high amounts of both fiber and n-3 PUFA-containing fish (HR: 0.57; 95% CI: 0.40, 0.82) [52]. Further, striking reciprocal changes in gut mucosal cancer risk biomarkers and microbiome were reported after African Americans were given a high-fiber, low-fat diet and rural Africans a high-fat, low-fiber Western-style diet [53]. Significantly increased butyrate production and reduced secondary bile acid concentrations were noted after the diet exchange to high-fiber, low-fat intake in African Americans [53]. A subsequent analysis in the Rotterdam prospective cohort lends support to the hypothesis that higher intakes of fat and fiber are important factors mediating the relationship between these variables. Increased risk of CRC was observed with n-3 PUFA intake when dietary fiber intakes were below the median, while fiber intakes above the median in combination with higher n-3 PUFA were associated with reduced risk [54]. Furthermore, when evaluated by food sources of n-3 PUFA, increased CRC risk was restricted to intake from non-marine sources. These mixed results for fat and fiber and CRC risk underscore the urgent need for controlled studies using

standardized intakes of fat and fiber subtypes and consideration of the potential impact of the gut microbiome.

Mechanisms of Action: Fat and Fiber Interaction

We conducted a series of seminal studies using both preclinical and *in vitro* models looking at molecular mechanism of action and providing strong evidence for a combined effect of types of fat and fiber in relation to colon tumorigenesis. The combination of bioactive components from fish oil (i.e., DHA and EPA n-3 PUFA) and prebiotic fermentable fibers (i.e., pectin) act synergistically to protect against colon cancer, in part, by enhancing apoptosis at the base of the crypt throughout all stages (initiation, promotion and progression) of colon tumorigenesis [34,55–60]. Interestingly, the combination of these agents was i) more effective in blocking tumorigenesis compared to either compound alone; ii) more effective compared to other fat (e.g., corn oil) and fiber (e.g., cellulose); iii) protective effects were due to increased apoptosis rather than decreased cell proliferation; and iv) the same phenotype emerged in both cancer and non-cancer cells [61]. Initially, the effects of fat (fish oil or corn oil; 15 g/100 g) and fiber (pectin or cellulose; 6 g/100 g) diets with and without carcinogen for 36 wks (2x2x2x2 factorial design; n=160 rats, 10/ group) were assessed with respect to colon cancer progression and various other aspects of colonocyte physiology [34,62]. Fish oil resulted in a significantly lower proportion of animals with adenocarcinomas relative to corn oil feeding (56% vs 70%, $P<0.05$). While pectin led to a lower incidence (57% vs 69%; NS), the combination of fish oil and pectin compared to corn oil and cellulose led to a greater reduction than fish oil alone (51% vs 76%, $P<0.05$) [34]. In addition, fish oil and pectin, alone and in combination, resulted in significantly higher colonic apoptotic indices compared to corn oil or cellulose [34,63]

Butyrate, produced from fermented fiber, induces apoptosis in tumor cells- as well as T-cells, the source of colonic inflammation [64], through inhibition of histone deacetylases (HDACi) and activation of the Fas receptor-mediated extrinsic death pathway [48,62,64–66]. HDACi occurs in a concentration-dependent manner and the butyrate concentration to which colonic epithelial cells are exposed is dependent on the gut microbiome. However, the role of butyrate in the induction of colonocyte apoptosis may be a secondary consequence to its ability to promote cellular oxidation. Butyrate induces cellular reactive oxygen species (ROS) when metabolized [61,67].. This is relevant because long-chain PUFA from fish oil (e.g., DHA, EPA) incorporated into cell membranes are susceptible to oxidation due to their high degree of unsaturation [35]. Lipid peroxidation can directly trigger release of pro-apoptotic factors from mitochondria into the cytosol [51]. To study ROS generation and antioxidant response via synergy between butyrate and n-3 PUFA, rats were fed corn oil +cellulose or fish oil+pectin. Colonocytes from rats fed fish oil+pectin had increased ROS, but reduced DNA damage [55]. Importantly, this enhanced oxidative stress, in particular membrane lipid oxidation, e.g., the formation of phospholipid hydroperoxides, was associated with exponentially increased programmed cell death [55,68–70]. These findings indicate that fish oil plus fermentable fiber modulate the redox environment, promoting lipid oxidation-mediated apoptosis, thus protecting the colon against oxidative stress. Consistent with this hypothesis, combined effects of n-3 PUFA and butyrate-induced apoptosis were partially blocked by co-incubation with a mitochondrial-targeted antioxidant [71], and

overexpression of glutathione peroxidase 4 (Gpx4), which catalyzes the reduction of hydrogen peroxide, organic hydroperoxides, and most specifically, lipid hydroperoxides [70]. This is particularly noteworthy, because the Gpx4-dependent peroxidation of PUFA in cell membranes has been linked to ferroptosis, a promising new mechanism to kill therapy-resistant cancers [72,73]. These novel findings suggest a regulated cell death nexus linking the metabolism of dietary fiber and n-3 PUFA, redox biology and cancer chemoprevention.

Since mitochondria play a key role in both apoptosis and necrosis by regulating energy metabolism, intracellular Ca^{2+} homeostasis, caspase activation and ROS release [74], we examined effects of DHA and butyrate on intracellular Ca^{2+} in mouse colonocytes [61]. Mitochondrial-to-cytosolic ratios were significantly increased compared to non-treated cultures; and a concomitant 43% increase in apoptosis compared to colonocytes treated with butyrate alone, but not DHA alone [61]. Complementary studies assessing whether DHA/butyrate-induced cell death is p53-mediated, established that Ca^{2+} accumulation serves as the trigger for programmed cell death in a p53-independent manner. DHA (but not EPA) and butyrate uniquely modulates intracellular Ca^{2+} compartmentalization and channel entry to induce colonocyte apoptosis. [48,51]. These data are consistent with the hypothesis that n-3 PUFA and butyrate together, compared to butyrate alone, enhance colonocyte programmed cell death by inducing a p53-independent, lipid oxidation-sensitive, mitochondrial Ca^{2+}-dependent (intrinsic) cell death pathway (Figure 1). Since the balance between cell proliferation and apoptosis is critical for maintaining a steady-state cell population, disruption of homeostatic mechanisms can result in clonal expansion and tumorigenesis. It is clearly established that colonic transformation of ademoma to carcinoma is associated with a progressive inhibition of apoptosis [34,75].

With respect to epigenetic programming, the effects of highly chemoprotective combination of fish oil and pectin on mouse colonic mucosal microRNA expression and their targets has been recently described [76]. The data indicate that this fat x fiber combination can modulate stem cell regulatory networks. In a complementary rat colon cancer progression model, the combinatorial diet (fish oil and pectin) uniquely modified global histone post-translational epigenetic programming, resulting in the upregulation of lipid catabolism and beta-oxidation associated genes [63] (Figure 2). Interestingly, emerging evidence indicates that colonocyte metabolism, e.g., mitochondrial beta-oxidation, determines the types of microbes that thrive in the gut [77,78]. Thus, dietary fat x fiber interactions may uniquely promote mechanisms that drive beta-oxidation induced hypoxia, thereby maintaining the growth of obligate anaerobic bacteria. This will help sustain a normal “healthy” symbiotic environment and stabilize mucosal barrier function [79].

Heterogeneity in Microbial Fermentation Capacity Affects Host Response to Dietary Fiber and Fat

Diet affects CRC risk in part by contributing particular substrates (e.g., dietary fiber, phytochemicals) that result in microbial production of chemoprotective metabolites and modulation of specific gut microbial species [80]. However, these dietary effects are also modulated by the metabolic capacity of the microbial community. We showed recently that

human colonic exfoliome gene expression response to a flaxseed lignan intervention depended on the composition of the microbial community at baseline prior to our intervention to modulate the production of the enterolignan, enterolactone [81]. The individuals that lacked the enterolactone microbial consortia never produced it during the intervention. Similarly, bacterial fermentation of dietary fibers and production of SCFA vary across individuals, driven partly by differences in gut microbial community structure and function [12]. Even in controlled feeding studies, where all participants receive the same food, substantial variation in fecal SCFA concentrations are reported [53,82].

A key factor in determining the availability of butyrate and setting apoptotic and other regulatory events in motion is the contribution of the gut microbiome to fiber fermentation. Types of complex carbohydrates consumed (e.g., dietary fibers, resistant starch) influence prevalence of certain consortia of gut bacteria and subsequent metabolites to which the host is exposed [83–96]. The microbiome responds rapidly to dietary interventions [97], although individual responses may differ [98–101]. Bacteria ferment fiber to SCFA, predominantly acetate, butyrate, and propionate, in a ratio of 3:1:1 [102] via metabolic pathways unique to anaerobic gut bacteria [103–106]. Butyrate producers form a functional cohort, rather than a monophyletic group, distributed across four different phyla: *Firmicutes, Fusobacteria, Spirochaetes,* and *Bacteroidetes* [107]. Butyrate is produced from fermentation via multiple pathways: the acetyl-CoA [21,108], glutarate [109–111], 4-aminobutyrate [112–114] and lysine pathways [115–117], but distribution of these pathways in the human microbiome varies [107].The dominant pathway associated with butyrate production is the acetyl-CoA pathway. The last step in conversion to butyrate across these multiple pathways is carried out by butyryl-CoA transferase (*but*) and butyrate kinase (*buk*) [107,118–120]. Acetate, often viewed as the final product of fermentation, supports syntrophy (cross-feeding) in the gut microbiome. For example, Roseburia spp. can condense acetate produced by other bacteria to produce butyrate via butyryl CoA: acetate CoA transferase and butyrate production is affected by the type of dietary fiber [121]. Vital et al [122] suggested that targeting specific human microbiome genes involved in butyrate production across these pathways gives a comprehensive picture of microbial butyrate production or “butyrogenic potential” in terms of gut resilience and a lower incidence of intestinal inflammation. These multiple pathways for bacterial production of butyrate ensure optimal butyrate availability to the host.

Methane-producing Archaea may also influence butyrate production in the gut [123]. Only a subset of healthy adult populations (~40%) harbor Archaea and among these individuals, an inverse association has been reported between fecal methanogen and butyrate concentrations [124]. Hydrogenotrophs, methanogens and eubacterial acetogens, compete for H_2 produced during fiber fermentation. The methanogens use H_2 to generate methane, whereas the acetogens use H_2 to reduce CO_2 to acetate via the acetyl-CoA pathway[125]. Because they lack butyrate kinase, these microbes can co-exist with other fermenters. Thus, the presence of methanogens may alter H_2 availability and contribute to differential exposure to butyrate and indirectly to CRC risk across populations [124].

Changes in Cancer-Pathway Measures with Fish Oil and SCFA in Healthy Humans

Mechanistic investigation of diet effects on apoptosis has been conducted primarily in colon cancer cell lines; although examples of *in vivo* changes in normal human colon with fish oil suggest that diet effects on healthy colonic mucosa are measurable. For example, individuals with a history of adenomas received one of two dietary interventions: i) 20% total fat; and increased n-3 PUFA via dietary fish + fish oil (~100 mg EPA + 400 mg DHA/d; n=21 experimental group); or ii) 20% total fat only (n=20, comparison). After 24 mos, the apoptotic index, Bax-positive cells, and Bax/Bcl-2 ratio were significantly increased in normal mucosa among those randomized to increased n-3 PUFA, whereas no change was observed in the comparison group [126]. In patients with resected polyps, EPA (2 g/d), supplementation for 3 mos resulted in higher apoptosis at the base of the crypt in normal colonic mucosa and significantly decreased cell proliferation, while no change was noted in the control group [127]. Finally, results of a recent dietary intervention suggest that distinct fat-fiber combinations have differential effects on cell proliferation in normal colonic mucosa [53]. Individuals with colorectal adenomas also have increased crypt cell proliferation and decreased apoptosis in macroscopically normal appearing colonic mucosa [127], and progressive inhibition of apoptosis in the transformation of normal colorectal mucosa to carcinoma [75]. These findings support the importance of an “etiologic field effect” in the colon [128], and the assertion that understanding effects of diet on cancer-related pathways in normal tissue is an *essential* part of cancer-prevention research.

Gut Microbiome, Diet and Tumorigenesis

While most dietary fat is absorbed in the small intestine, some enters the colonic lumen. High-fat diets rich in saturated fats (Western diet) alter gut microbial composition with negative health outcomes [129–132]. In contrast, recent studies suggest that high n-3 PUFA influence the gut microbiome favorably or has no negative health effects [133,134]. Exposure to EPA and DHA increases *Lactobacillus* and *Bifidobacteria* and reduces *Helicobacter and Fusobacteria nucleatum*. [133–138], –important prebiotic effects given that increases in *Lactobacillus* and *Bifidobacteria* are associated with reduced inflammation [139–142]. Both *Helicobacter* and *F. nucleatum* are pathogens and n-3 PUFAs can act as antibacterial or bacteriostatic compounds. Differential susceptibility of bacteria to n-3 PUFAs is likely to be due to their ability to permeate the outer membrane or cell wall, which will enable access to the sites of action on the inner membrane leading to membrane disruption. Studies also suggest associations between specific microbes and CRC may be associated with diet [143]. *Fusobacterium nucleatum* has been shown to promote colorectal tumor growth and inhibit antitumor growth in animal models and is detected in a subset of human colorectal neoplasias [144]. In a large prospective cohort using data from the Nurse’s Health Study and Health Professionals Follow-up Study, diets rich in whole grains and dietary fiber are associated with a lower risk for *F nucleatum*–positive, but not *F nucleatum*–negative, CRC, supporting a potential role for gut microbiota in mediating the association between diet and colorectal neoplasms [145].

Conclusions

Studies in animals have shown that both n-3 PUFA and a bacterial metabolite of dietary fiber (butyrate) may reduce colon tumor formation, and that the two in combination are even more effective than either alone. Several novel mechanisms of action have been suggested, including the enhancement of a Gpx4-dependent, lipid oxidation-sensitive, Gpx-4 and mitochondrial dependent cell death pathway in the colonic mucosa. In humans, some epidemiologic studies suggest that people who consume high-fiber diets or use n-3 PUFA supplements may have a lower risk of CRC, however there are currently no controlled dietary interventions evaluating the combined effects of these two dietary constituents on CRC-relevant pathways in humans. Data from preclinical and mechanistic studies support an important role for gut microbe-derived SCFA, particularly butyrate, in combination with n-3 PUFA, in reduction of colon tumorigenesis. However, although both n-3 PUFA [34,146–149], and fiber [150–153], alone have been studied, no clinical studies have been conducted to translate these combinatorial findings to humans. We propose that low intakes of fiber and n-3 PUFA in Western populations, and the failure to address an interaction, may explain why the chemoprotective effects of n-3 PUFA and fermentable fibers are not detected consistently in prospective cohort studies.

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Key Points:

- n-3 PUFA and butyrate from bacterial fiber fermentation may reduce colorectal cancer risk
- fat and fiber interaction (pescovegetarian diet) induces intrinsic mitochondrial-mediated programmed cell death in the colon, which reduces colorectal cancer risk
- fish oil and fermentable fiber intake uniquely promote mucosal beta-oxidation which maintains a hypoxic environment in the gut and promotes the growth of obligate anaerobic bacteria, thereby inhibiting dysbiotic microbial expansion

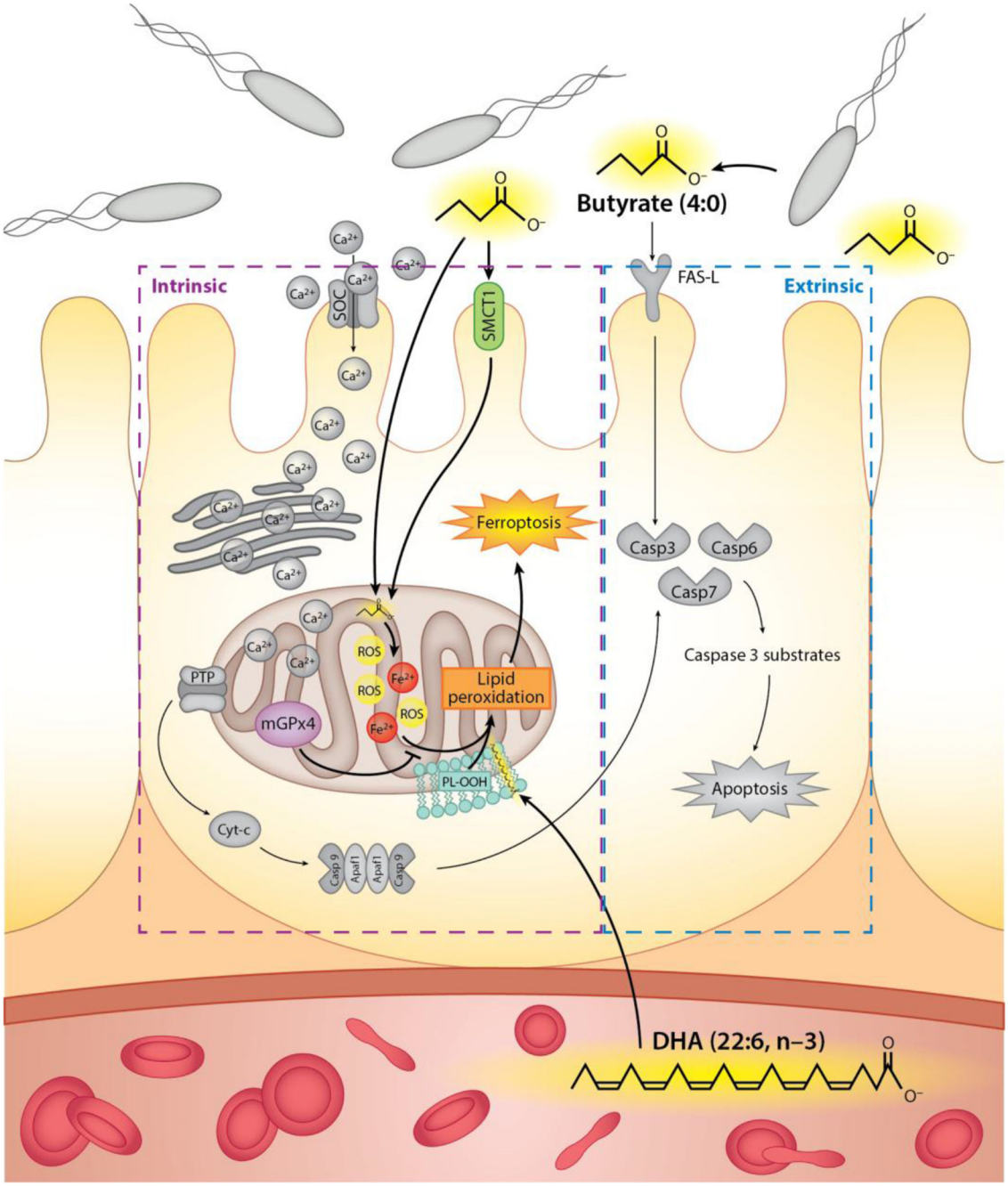

Figure 1. Proposed mechanisms by which supplemental n-3 PUFA and butyrate from bacterial fiber fermentation may reduce cancer risk.

n-3 PUFA + fermentable fiber will attenuate mitochondrial anti-oxidant defenses and promote colonocyte mitochondrial Ca^{2+} and Gpx4-dependent ferroptosis, a form of intrinsic programmed cell death. Increased butyrate exposure will also extrinsically alter cancer-related pathways in a CRC chemopreventive direction.

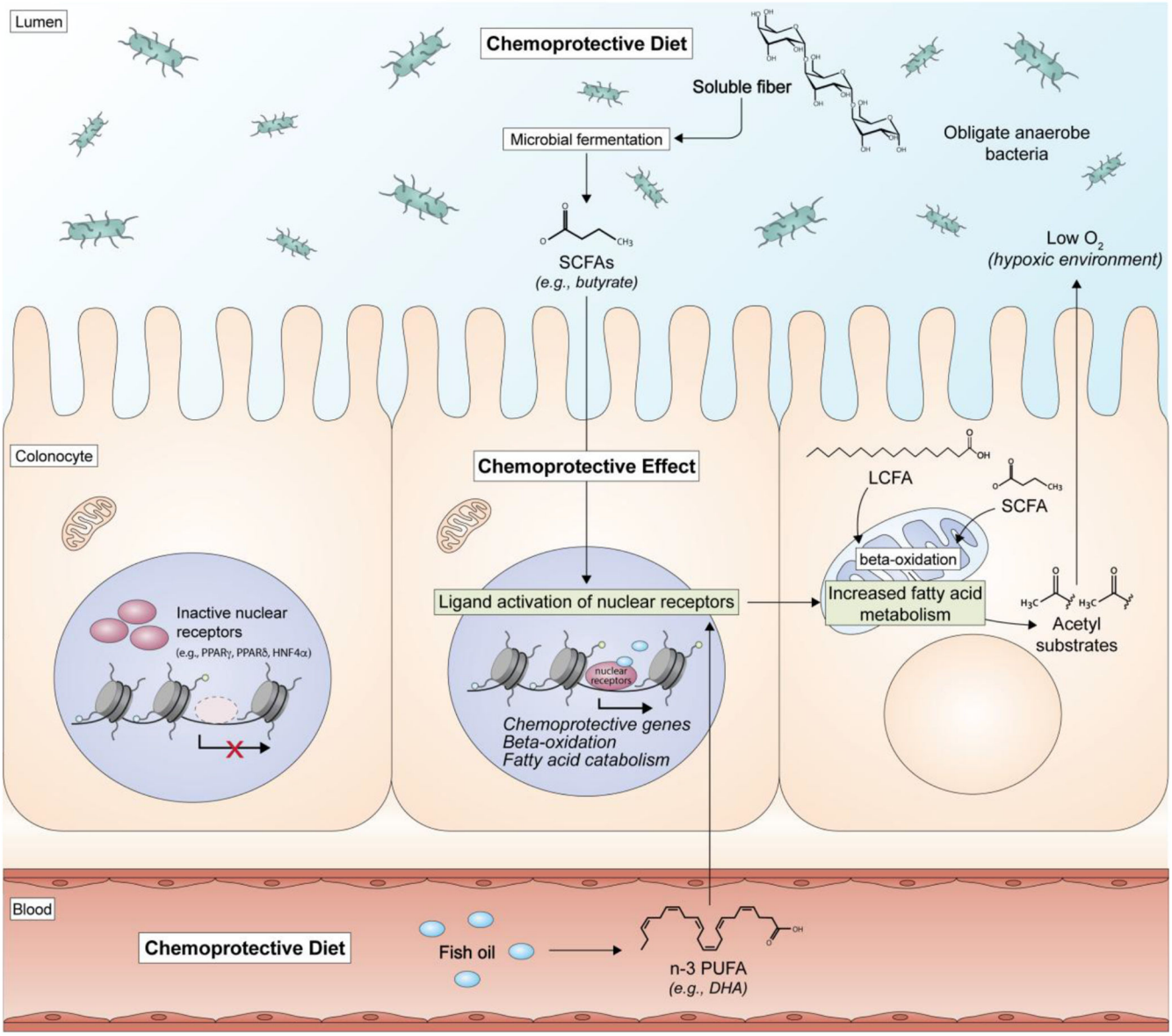

Figure 2. Putative epigenetic effects of n-3 PUFA and fermentable fiber on global histone post-translational epigenetic programming in the colon.

The pescovegetarian diet (n-3 PUFA from fish and dietary fiber) upregulates EPA and DHA ligand-dependent nuclear receptors. Transcriptional events are further enhanced by the increased production of butyrate via fiber fermentation, which directly and indirectly modifies histone acetylation. These combinatorial effects enhance the mitochondrial L-carnitine shuttle, inhibit lipogenesis and promote the accumulation of acetyl CoA-dependent beta-oxidation. The enhanced mucosal beta-oxidation maintains a hypoxic environment in the gut and promotes the growth of obligate anaerobic bacteria and inhibits dysbiotic microbial expansion.