REVIEW

Potential of Omega-3 Polyunsaturated Fatty Acids in Managing Chemotherapy- or Radiotherapy-Related Intestinal Microbial Dysbiosis

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ABSTRACT

Chemotherapy- or radiotherapy-related intestinal microbial dysbiosis is one of the main causes of intestinal mucositis. Cases of bacterial translocation into peripheral blood and subsequent sepsis occur as a result of dysfunction in the intestinal barrier. Evidence from recent studies depicts the characteristics of chemotherapy- or radiotherapy-related intestinal microbial dysbiosis, which creates an imbalance between beneficial and harmful bacteria in the gut. Decreases in beneficial bacteria can lead to a weakening of the resistance of the gut to harmful bacteria, resulting in robust activation of proinflammatory signaling pathways. For example, lipopolysaccharide (LPS)-producing bacteria activate the nuclear transcription factor-κB signaling pathway through binding with Toll-like receptor 4 on stressed epithelial cells, subsequently leading to secretion of proinflammatory cytokines. Nevertheless, various studies have found that the omega-3 (n–3) polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid and eicosapentaenoic acid can reverse intestinal microbial dysbiosis by increasing beneficial bacteria species, including *Lactobacillus*, *Bifidobacterium*, and butyrate-producing bacteria, such as *Roseburia* and *Coprococcus*. In addition, the n–3 PUFAs decrease the proportions of LPS-producing and mucolytic bacteria in the gut, and they can reduce inflammation as well as oxidative stress. Importantly, the n–3 PUFAs also exert anticancer effects in colorectal cancers. In this review, we summarize the characteristics of chemotherapy- or radiotherapy-related intestinal microbial dysbiosis and introduce the contributions of dysbiosis to the pathogenesis of intestinal mucositis. Next, we discuss how n–3 PUFAs could alleviate chemotherapy- or radiotherapy-related intestinal microbial dysbiosis. This review provides new insights into the clinical administration of n–3 PUFAs for the management of chemotherapy- or radiotherapy-related intestinal microbial dysbiosis. *Adv Nutr* 2019;10:133–147.

Keywords: chemotherapy, radiotherapy, intestinal mucositis, dysbiosis, omega-3 polyunsaturated fatty acid

Introduction

Intestinal mucositis is the main lesion that develops after chemotherapy or abdominal radiotherapy (1). Both ionizing radiation and chemical reagents target the rapid renewal of crypt cells, ultimately resulting in de-epithelialization (2, 3). Patients with acute chemotherapy- or radiotherapy-induced intestinal mucositis present with symptoms including abdominal pain, vomiting, diarrhea, and digestive dysfunctions, whereas the late-onset toxicities of ionizing irradiation to the gut include fistula formation, obstruction, or even perforation (4, 5). These side effects severely affect the quality of life of these patients.

Dysbiosis denotes any change in the composition of resident commensal communities relative to the communities found in healthy individuals (6). Herein, microbial dysbiosis is characterized by a decrease in beneficial microbes, an overgrowth of harmful microbes, and a loss of microbial diversity (6). To date, it is accepted that chemotherapy or radiotherapy can cause intestinal microbial dysbiosis (7). By reviewing recent studies, Touchefeu et al. (7) reported that

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Abbreviations used: CRC, colorectal cancer; G-CSF, granulocyte colony-stimulating factor; iNOS, inducible NO synthase; IκB, inhibitor of κB; MDA, malondialdehyde; Nrf2, nuclear factor erythroid 2 p45–related factor 2; PK, protein kinase; ROS, reactive oxygen species; sIgA, secretory IgA; TLR, Toll-like receptor; 4-OHE, 4-oxo-2-nonenal.

the intestinal microbial dysbiosis induced by chemotherapy and by abdominal radiotherapy could be characterized by decreased proportions of *Clostridium cluster* XIVa, *Faecalibacterium prausnitzii*, and *Bifidobacterium* and increased proportions of *Enterobacteriaceae* and *Bacteroides*. In healthy individuals, the commensal bacteria assist the hosts in improving their defense against harmful bacteria (8, 9). However, intestinal microbial dysbiosis alone is sufficient to initiate inflammation within the intestine (10). For example, LPS from *Escherichia coli* activates the NF-κB signaling pathway, which leads to high secretions of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6 by stressed cells (11–13).

Clinically, the available drugs for treating intestinal mucositis after chemotherapy or radiotherapy include glutamine, sucralfate, and antibiotics (7). The omega-3 (n–3) PUFAs, including EPA and DHA, exhibit therapeutic potential for some autoimmune diseases such as inflammatory bowel disease and rheumatoid arthritis through their anti-inflammatory and antioxidant functions and through maintaining the integrity of the intestinal epithelium (14–17). In addition, n–3 PUFAs are able to reduce intestinal microbial dysbiosis through increasing the proportions of beneficial bacteria and decreasing the proportions of pathogenic bacteria and their products in the gut (18, 19). Moreover, results from both basic and clinical studies have confirmed the anticancer effects of n–3 PUFAs (20). On this basis, the use of n–3 PUFAs is an optional strategy for managing patients with intestinal microbial dysbiosis, especially in those patients undergoing chemotherapy or radiotherapy. In this review, we introduce the composition of the commensal microbiota in the healthy gut, after which we summarize the characteristics of chemotherapy- or radiotherapy-related intestinal microbial dysbiosis and explain the pathogenesis of mucositis associated with intestinal microbial dysbiosis. Next, by reviewing the current findings on improving beneficial gut bacteria, attenuating proinflammatory responses, and inhibiting tumor growth with n–3 PUFAs, we show the potential for managing patients experiencing chemotherapy- or radiotherapy-related intestinal microbial dysbiosis with the use of n–3 PUFAs. Taken together, we provide new insights into the clinical use of n–3 PUFAs for patients with abdominal cancer with chemotherapy- or radiotherapy-related intestinal microbial dysbiosis.

Composition of Commensal Bacteria in the Human Intestinal Tract

In healthy individuals, the number of species of commensal bacteria in the gut ranges from 500 to 1000 because the selection pressure in the gut restricts bacterial diversity (21). Within the gut, phyla including *Bacteroidetes* and *Firmicutes* account for ~98% of intestinal microflora (21, 22). By contrast, *Proteobacteria*, *Actinobacteria*, and *Fusobacteria* account for <1% (23). However, gut microbe composition varies among healthy individuals (24). Nevertheless, the proportions of anaerobes are overwhelmingly superior to the aerobes in a healthy gut (25) because the microenvironment in a heathy gut is anoxic, thus benefiting the growth of anaerobes (26), such as *Bacteroides* and *Bifidobacterium* (27). For the distribution of intestinal microflora, the small intestine is dominated by *Firmicutes* and *Actinobacteria* and the colon is dominated by *Bacteroidetes* and the *Lachnospiraceae* family (28). Collectively, the above information suggests that the composition of commensal bacteria is well orchestrated in the gut.

Specific Effects of Intestinal Commensal Bacteria on Gut Homeostasis

The intestinal commensal bacteria are crucial in maintaining gut homeostasis (29). As documented, the intestinal commensal bacteria function in several ways, such as modulating nutrient metabolism and absorption, maintaining epithelial homeostasis, and improving gut immune tolerance (21, 29, 30).

The gut is the main site of food digestion, in which dietary nutrients are metabolized and absorbed. Intestinal commensal bacteria are important contributors to these processes. By taking advantage of dietary nutrients, the commensal bacteria are able to produce essential substances benefiting human health, such as vitamin B-12 (31), vitamin K-2 (32), and several essential amino acids (33). Similarly, fermentation of dietary fibers by anaerobes including *Lactobacillus* and butyrate-producing bacteria allows these microbes to produce SCFAs, which include acetic acid, butyric acid, and propionic acid (30, 34). The SCFAs can be consumed by enterocytes for intracellular energy production, thus facilitating the biochemical processes (30, 33–35). Moreover, the commensal bacteria participate in the metabolism of bile acids. In this case, primary bile acids can be converted into >20 different secondary bile acid metabolites, which facilitate dietary lipid turnover and absorption (36). In addition, a vegetarian diet is rich in polyphenols (37). To achieve an appropriate bioavailability of dietary polyphenols, the gut microbiota function in metabolizing such polyphenols into absorbable compounds (37). For example, equol, a metabolite of the soya isoflavone daidzein, exhibits its high affinity toward estrogen receptor (ER), thus provoking the biological effects by the interaction between equol and ER (37).

In addition to nutrient metabolism and absorption, the intestine serves a barrier function, because it is the intestinal epithelium that separates the human body from the outside environment. To avoid epithelial injury, *Lactobacillus* forms a biofilm covering the epithelium to separate the pathogen-associated receptors on enterocytes from harmful bacteria in the gut (38). And *Streptococcus thermophiles* can produce lactic acid to inhibit the growth of harmful bacteria by decreasing the pH of the intestinal tract (39). Moreover, the commensal bacteria help maintain the integrity of the intestinal epithelium. For example, *Lactobacillus* can stimulate the biosynthesis of heat-shock protein 72 within enterocytes in a p38 mitogen-activated protein kinase (p38/MAPK)–dependent manner, leading to an increased tolerance of enterocytes toward foreign stimuli (40). In addition, the SCFAs

produced by *Lactobacillus* or by butyrate-producing bacteria function in improving epithelial homeostasis (30, 33–35). By taking advantage of SCFAs, the intestinal epithelial cells upregulate their expressions of genes related to cell differentiation and proliferation (33, 34). Meanwhile, upon SCFA stimulation, goblet cells can increase their mucus production and secretion (30, 33, 35). Moreover, SCFAs protect intestinal epithelial cells against oxidative stress–induced apoptosis (31). In addition to these effects, SCFAs exert several other impacts on intestinal barrier, such as the inhibition of NF-κB, activation of inflammasomes and subsequent production of IL-18, increased secretion of secretory IgA (sIgA) by B cells, and increased proportions of T-regulatory cells and tolerogenic dendritic cells in the intestine (30). In this aspect, the SCFA-producing bacteria are crucial to inducing gut immune tolerance toward lumen antigens. However, when being challenged with chemotherapy or radiotherapy, intestinal microbial dysbiosis commonly occurs (7). In this context, *Lactobacillus* or butyrate-producing bacteria were decreased in the gut (41, 42), thus weakening the intestinal barrier function.

Chemotherapy- or Radiotherapy-Related Intestinal Microbial Dysbiosis and Mucositis Development

Characteristics of chemotherapy- or radiotherapy-related intestinal microbial dysbiosis

The pathogenesis of intestinal mucositis after chemotherapy or radiotherapy is complicated (43, 44). Herein, chemotherapy- or radiotherapy-related intestinal microbial dysbiosis enables proinflammatory responses within the gut to be sustained (7). Commonly, chemotherapy- or radiotherapy-related intestinal microbial dysbiosis is characterized by an imbalance in the proportions of beneficial bacteria and harmful bacteria, perhaps even presenting as an absolute dearth of beneficial bacteria and overreproduction of harmful bacteria in the gut (7). With regard to the contributions of intestinal microbial dysbiosis to the pathogenesis of mucositis, it has been shown that oral delivery of feces from enteritic mice caused germ-free mice to become predisposed to colitis induced by dextran sulfate sodium (45). Moreover, the germ-free mice were more resistant to ionizing irradiation than conventional mice (46) because turnover of the intestinal epithelium in germ-free mice is impaired due to the lack of commensal bacteria, which contribute to epithelial self-renewal in conventional mice (47). As noted above, both ionizing irradiation and chemical reagents selectively kill the expanding cells within crypts (2, 3). Alternatively, even in the case of intestinal microbial dysbiosis, several species of harmful bacteria, such as *E. coli* (48) and *Fusobacterium* (49), have been shown to stimulate epithelial turnover in conventional mice.

Clinically, remarkable alterations in the constitution of the intestinal microbiota are observed after chemotherapy or radiotherapy (**Table 1**). Such alterations are associated with dysfunctions of the intestinal barrier. In the intestinal microbial dysbiosis induced by abdominal radiotherapy, compared with patients without diarrhea, patients with diarrhea symptoms presented with a higher abundance of *Bacteroides*, *Escherichia*, and *Megamonas* in their feces (42). Likewise, a decline in the fecal proportion of members of the *Firmicutes* phylum is also a typical feature of intestinal microbial dysbiosis induced by chemotherapy and pelvic radiotherapy (51, 52). In addition, Wang et al. (42) determined that if the 16S ribosomal RNA ratios of *Firmicutes* to *Bacteroides* in feces were >2.15 in patients before receiving abdominal radiotherapy, it would predict that they were more susceptible to enteritis than patients with ratios <1.79, suggesting that the ratio of *Firmicutes* to *Bacteroides* could be used as an indicator of enteritis. Nevertheless, on the basis of recent data, we propose that this indicator may not be applicable to patients with long-term intake of antibiotics or those with inflammatory bowel disease due to the pre-existing intestinal microbial dysbiosis in these patients before cancer treatment (6). Moreover, the patients with diarrhea exhibited sharp elevations in serum LPS after abdominal radiotherapy as well. For the alterations in intestinal microbiota after chemotherapy, Montassier et al. (50) identified that the feces of these patients contained high proportions of *Proteobacteria* and *Enterobacteriaceae*, thus resulting in metabolic disorders of nucleotides, energy, and vitamins among these patients. In addition, among the patients with diarrhea after chemotherapy, there were decreased amounts of *Lactobacillus* and *Bifidobacterium* in the feces, with accompanying increased proportions of *E. coli* and *Staphylococcus* (41). However, from the published literature, evidence suggesting that radiotherapy can significantly alter the fecal proportions of *Lactobacillus* and *Bifidobacterium* is still unavailable (42, 52, 54).

Chemotherapy- or radiotherapy-related intestinal microbial dysbiosis provokes the proinflammatory events in the lesioned gut

The robust activation of the NF-κB signaling pathway by the interactions between the ligands of Toll-like receptors (TLRs) and TLRs on enterocytes contributes significantly to the disordered milieu present within the inflammation of a lesioned gut (55). The TLR ligands of gut microbes are recognized by the TLRs on enterocytes; in this context, downstream transcriptional factors of the NF-κB family alter their target genes, which ultimately provokes the stressed cells to produce different inflammatory cytokines (56). For example, when being challenged with chemotherapy or radiotherapy, TLR4 drives the secretions of IL-1β, TNF-α, and IL-6 by enterocytes corresponding to LPS-producing bacteria (11–13, 57). This underlying mechanism is shown in **Figure 1**. Recently, the specific relation between radiation-induced intestinal microbial dysbiosis and the host secretion of IL-1β was identified by Gerassy-Vainberg et al. (45). They found that 3 dominant bacterial phyla—*Proteobacteria, Verrucomicrobia*, and *Firmicutes*—had altered proportions in an irradiated gut. By using the genera classification method, *Akkermansia* in the *Verrucomicrobia* phylum was found to

TABLE 1 Characteristics of chemotherapy- or radiotherapy-related dysbiosis[1]

Study, year (ref)	Disease/no. of patients	Chemo- or radiotherapy	Bacteria-detecting techniques	Samples	Main findings
Wang et al., 2015 (42)	Cervical cancer/8 Anal cancer/1 Colorectal cancer/2	Pelvic radiotherapy DT: 44 ~ 50 Gy in 22 ~ 25 fractions	454 Pyrosequencing	Feces	• Bacterial phylum: *Firmicutes* vs. *Bacteroidetes* ratio ↓ • Bacterial family: *Lachnospiraceae* ↓ • Bacterial genus: *Faecalibacterium* ↓, *Oscillibacter* ↓, *Roseburia* ↓, *Streptococcus* ↓, *Clostridium* XIVa ↑, *Bacteroides* ↑ • Diarrhea vs. no diarrhea: *Clostridium* XIVa ↓, *Sutterella* ↓
Montassier et al., 2015 (50)	Non-Hodgkin lymphoma/28	Chemotherapy	454 Pyrosequencing	Feces	• Bacterial phylum: *Firmicutes* ↓, *Actinobacteria* ↓, *Proteobacteria* ↑ • Bacterial family: *Enterococcaceae* ↑, *Enterobacteriaceae* ↑ • Bacterial genus: *Ruminococcus* ↓, *Oscillospira* ↓, *Blautia* ↓, *Lachnospira* ↓, *Roseburia* ↓, *Dorea* ↓, *Coprococcus* ↓, *Anaerostipes* ↓, *Clostridium* ↓, *Collinsella* ↓, *Adlercreutzia* ↓, *Bifidobacterium* ↓, *Citrobacter* ↑, *Klebsiella* ↑, *Enterococcus* ↑, *Megasphaera* ↑, *Parabacteroides* ↑ • Capacities of metabolism: energy metabolism ↓, cofactors metabolism ↓, vitamins metabolism ↓, glycan metabolism ↑, signal transduction ↑, xenobiotics biodegradation, ↑
Montassier et al., 2014 (51)	Non-Hodgkin lymphoma/8	Chemotherapy	454 Pyrosequencing	Feces	• Bacterial phylum: *Firmicutes* ↓, *Actinobacteria* ↓, *Firmicutes* vs. *Bacteroidetes* ratio ↓, *Proteobacteria* ↑, *Bacteroidetes* ↑ • Bacterial genus: *Blautia* ↓, *Faecalibacterium* ↓, *Roseburia* ↓, *Bacteroides* ↑, *Escherichia* ↑
Nam et al., 2013 (52)	Gynecological cancer/9	Pelvic radiotherapy DT: 50.4 Gy in 28 fractions	454 Pyrosequencing	Feces	• Bacterial phylum: *Firmicutes* ↓, *Fusobacterium* ↑ • Bacterial family: *Eubacteriaceae* ↓, *Fusobacteriaceae* ↑, *Streptococcacea* ↑
Stringer et al., 2013 (41)	Colorectal cancer/11 Breast cancer/2 Melanoma/1 Healthy volunteers/2	Chemotherapy	qPCR	Feces	• Bacterial genus: *Lactobacillus* ↓, *Bacteroides* ↓, *Bifidobacterium* ↓, *Enterococcus* ↓, *Staphylococcus* ↑ • Bacterial species: *Escherichia coli* ↑
Zwielehner et al., 2011 (53)	Leukemia/5 Myeloma/2 Non-Hodgkin lymphoma/3 Gastrointestinal cancer/3 Breast cancer/1 Thymus cancer/1 Urothelial cancer/1 Ovarian cancer/1	Chemotherapy	Bacterial 16S-sequencing	Feces	• Bacterial genus: *Bifidobacteria* ↓, *Lactobacillus* ↓, *Veillonella* ↓, *Clostridium* cluster XIVa ↓, *Bacteroides* ↑, *Clostridium* cluster IV ↑ • Bacterial species: *Faecalibacterium prausnitzii* ↑, *Enterococcus faecium* ↑, *Clostridium difficile* ↑
Manichanh et al., 2008 (54)	Abdominal tumors/10 Healthy controls/5	Abdominal radiotherapy DT: 43.2~54.0 Gy in 25 fractions	Bacterial 16S-sequencing	Feces	• Bacterial phylum: *Actinobacteria* ↑ • Bacterial class: *Bacilli* ↑, *Clostridia* ↓

[1] DT, dose in total; ref, reference; ↓, decreased; ↑, increased.

be abundant, as was *Sutterella* in the *Proteobacteria* phylum. Among these bacteria, the proportions of *Proteobacteria* and *Verrucomicrobia* were increased, whereas the proportion of *Firmicutes* was decreased in the gut. Such alterations were highly associated with an increased secretion of IL-1β by the host. Moreover, when these irradiated mice were administered their own feces orally, the concentration of IL-1β within the lesioned colonic tissue increased further (45). Moreover, some anti-inflammatory bacteria, such as *F. prausnitzii* and *Bifidobacterium* (8, 58), decreased their amounts, or even disappeared after chemotherapy (50, 59). In this context, the proinflammatory events could become robust partially due to a lack of *F. prausnitzii* and *Bifidobacterium*, which could induce host secretion of IL-10 (58) and antagonize inhibitor of κB (IκB) degradation by producing the nonlipophilic compounds (8), respectively.

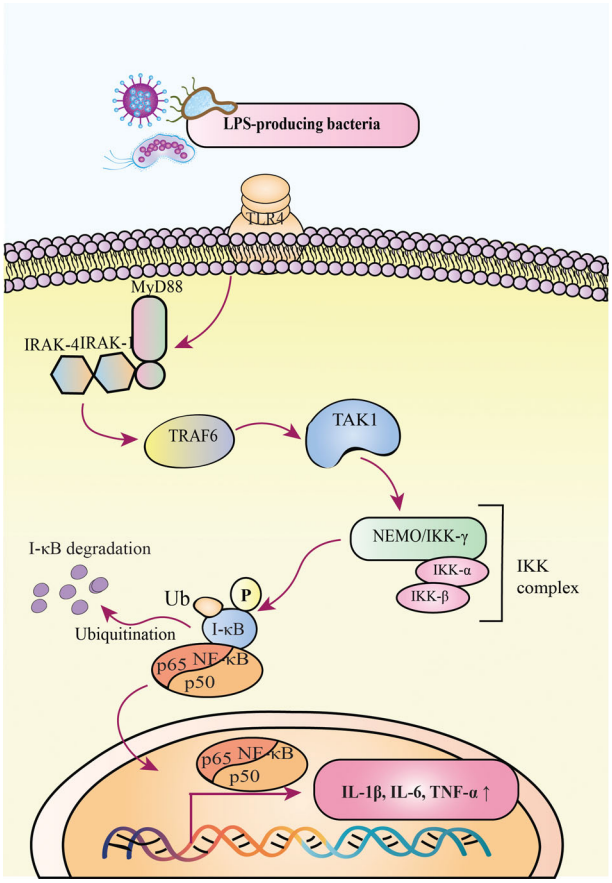

FIGURE 1 LPS-TLR4 activates the NF-κB signaling pathway. During this process, MyD88 is recruited to TLR4. Then, IRAKs and TRAF6 are activated step by step. Herein, TRAF6 activates the TAK1 molecule, which is essential for subsequent activation of the IKK complex. The IKK complex can phosphorylate the IκB molecule, which ultimately undergoes ubiquitination and degradation. Then, the NF-κB, consisting of the subunits p50 and p65, will translocate into the nucleus to initiate the transcriptions of genes encoding IL-1β, IL-6, and TNF-α. IKK, inhibitor of κB kinase; IRAK, IL-1 receptor–associated kinase; I-κB, inhibitor of κB; MyD88, myeloid differentiation factor 88; NEMO, NF-κB essential modulator; P, phosphorylation; TAK1, TGF-β–activated kinase 1; TLR4, Toll-like receptor 4; TRAF6, TNF receptor–associated factor 6; Ub, ubiquitination; ↑, increase.

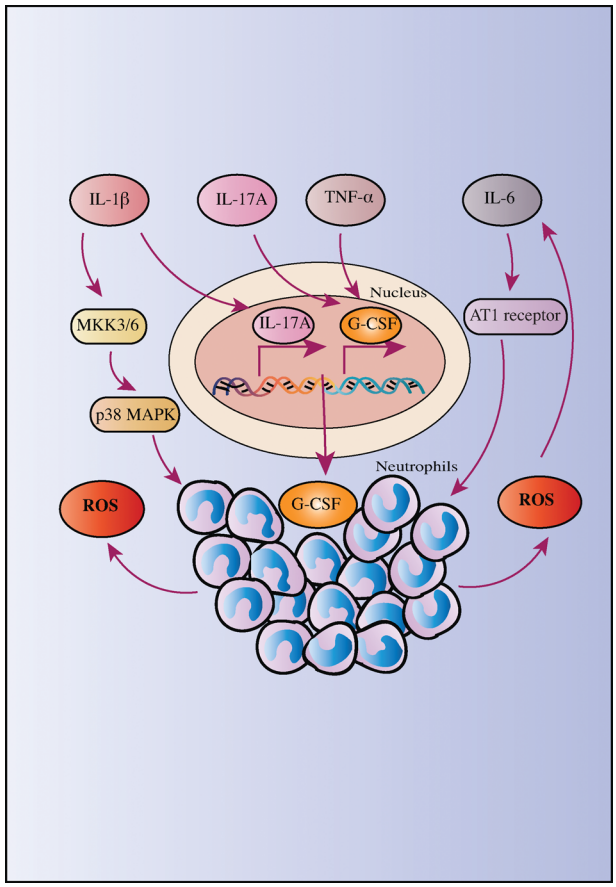

FIGURE 2 Inflammation provokes oxidative stress. Proinflammatory cytokines, such as IL-1β, IL-6, IL-17A, and TNF-α, can increase oxidative stress by recruiting neutrophils as well as inducing neutrophils to produce ROS. AT1 receptor, angiotensin II type 1 receptor; G-CSF, granulocyte colony-stimulating factor; MKK3/6, mitogen-activated protein kinase kinase 3/6; p38 MAPK, p38 mitogen-activated protein kinase; ROS, reactive oxygen species.

Similarly, *Ruminococcus*, *Coprococcus*, *Dorea*, and *Roseburia* have been reported to be capable of inhibiting the activation of the NF-κB signaling pathway among stressed enterocytes (60). If these bacteria were absent after chemotherapy or radiotherapy, intestinal inflammation potentially increased.

Chemotherapy- or radiotherapy-related intestinal microbial dysbiosis increases oxidative stress

After chemotherapy or radiotherapy, intestinal inflammation is followed by oxidative stress, because some proinflammatory cytokines are capable of triggering the production of oxyradicals (Figure 2). For example, IL-1β is capable of inducing neutrophils to release superoxide through activation of the p38/MAPK signaling pathway (61). In addition, IL-1β could stimulate the T-helper 17 (Th17) cells to produce IL-17A (62), which would aggravate the oxidative stress through increasing endogenous secretion of granulocyte colony-stimulating factor (G-CSF) (63). Likewise, TNF-α could upregulate the expression of the gene encoding G-CSF in stressed fibroblasts (64). G-CSF is a potent neutrophil-recruiting cytokine, which could clear lesioned cells or bacterial infection by releasing reactive oxygen species (ROS) (65). Before infiltrating into lesioned sites, the circulating neutrophils must pass through the microvascular wall to reach their destination. IL-1β is also capable of upregulating the expression of the gene encoding inducible NO synthase (iNOS), thus enabling an increase in capillary permeability by promoting the production of NO within the endothelium (66). IL-6 is capable of promoting superoxide production via upregulation of the expression of the gene encoding the angiotensin II type 1 receptor on endothelial cells (67). In return, such ROS stimulate IL-6 secretion by inducing caveolin-1 to bind with Sirtuin 1 (Sirt1), therefore leading to the inactivation of Sirt1 (68). From this aspect,

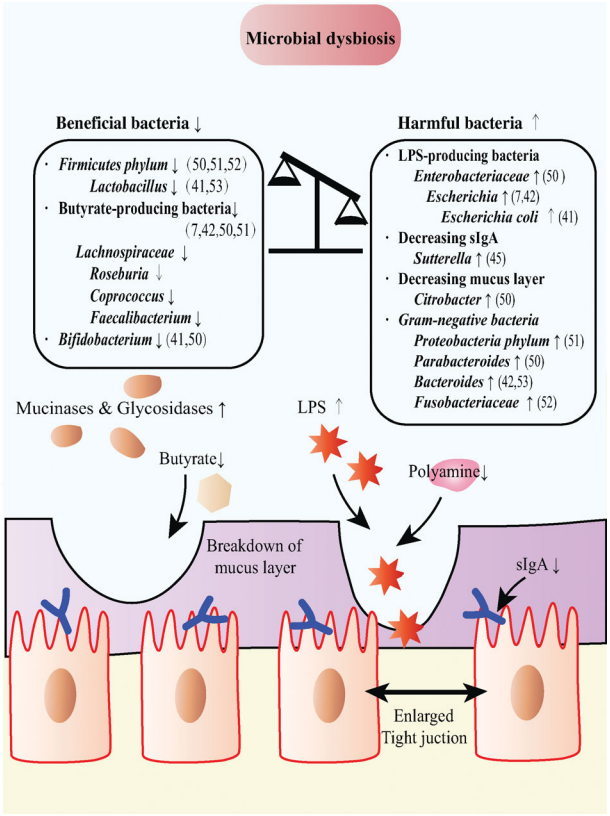

FIGURE 3 Chemotherapy- or radiotherapy-related intestinal microbial dysbiosis leads to dysfunction in the intestinal barrier. First, the intestinal barrier can be compromised by LPS-producing bacteria, leading to increased permeability. Second, the reduced proportion of butyrate-producing bacteria enables the mucus layer to be thinner than before. Third, gut concentrations of sIgA are decreased after chemotherapy or radiotherapy. sIgA, secretory IgA; ↑, increased; ↓, decreased.

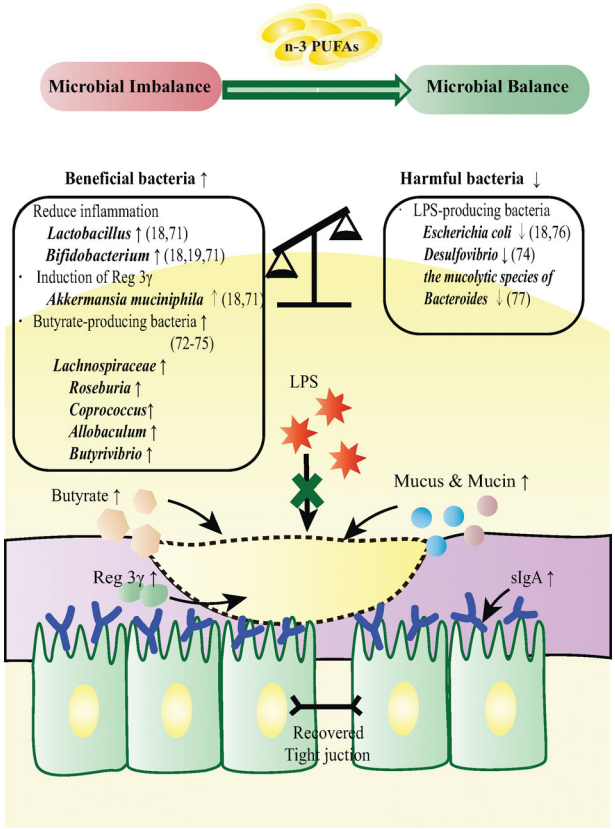

FIGURE 4 n–3 PUFAs attenuate chemotherapy- or radiotherapy-related intestinal microbial dysbiosis. n–3 PUFAs revert chemotherapy- or radiotherapy-related dysbiosis and maintain the intestinal barrier. Intake of n–3 PUFAs restores the beneficial microbiota via increasing the proportions of beneficial bacteria and reducing the proportions of harmful bacteria. As a result, the mucus layer is consolidated, intestinal permeability is reduced, and the concentration of sIgA is restored. Reg 3γ, regenerating islet derived protein 3γ; sIgA, secretory IgA; ↑, increased; ↓, decreased.

the inflammation and oxidative stress after chemotherapy or radiotherapy mutually aggravate the milieu within the lesioned gut.

Chemotherapy- or Radiotherapy-Related Intestinal Microbial Dysbiosis and Deficiency of the Intestinal Barrier

The epithelial layer is known to be an important component of the mucosal barrier. In heathy individuals, tight junctions between epithelial cells play a pivotal role in maintaining the permeability of the intestinal epithelium, allowing for nutrient absorption while sequestering harmful substances to the lumen (69). In addition, the mucus layer covering the intestinal epithelium also contributes to mucosal barrier function. This layer consists of glycoproteins, mucins, immunoglobulins, and butyrate (34, 35, 70) (Figures 3 and 4). For example, mucin trimers build a biofilm that protects the epithelial cells from lumen toxins (78), and sIgA is a very important antibody able to neutralize toxins and pathogens in the mucus layer (70). In a healthy gut, some beneficial bacteria such as *Lactobacillus* and *Streptococcus* have been reported to promote the biosynthesis of sIgA, (79). Butyrate is able to promote mucin synthesis by upregulating the expression of the mucin 2 (*MUC2*) gene (80). In addition, butyrate is capable of promoting the secretion of cathelicidin, an antimicrobial peptide released by intestinal epithelial cells (81). Hence, butyrate-producing bacteria play a key role in maintaining the physiologic composition of mucus in a healthy gut. With these processes, the intestinal barrier is well maintained, thus improving the host's defense against lumen pathogens. However, when challenged by chemotherapy- or radiotherapy-related intestinal microbial dysbiosis, the permeability of the intestinal epithelium is increased and the mucus layer is interrupted to a certain extent due to intestinal microbial dysbiosis. In addition, the mucositis after chemotherapy or radiotherapy is always accompanied by impaired barrier function (Figure 3).

Chemotherapy- or radiotherapy-related intestinal microbial dysbiosis increases intestinal permeability

Intestinal microbial dysbiosis can increase intestinal permeability. For example, LPS has been shown to be capable of

increasing intestinal permeability, which was mediated by an increased expression of TLR4 by enterocytes (Figure 3) (82). In addition to LPS, IL-1β could disrupt the tight junctions among epithelial cells by increasing the intracellular production of myosin light chain kinase (MLCK) (83). MLCK is capable of phosphorylating the myosin light chain (MLC) at serine residue 19 (84). The phosphorylated MLC subsequently activates Mg^{2+}-myosin ATPase, resulting in the contraction among perijunctional actomyosin filaments and a widening of the intercellular spaces (83). However, if further challenged with chemotherapy, the epithelial permeability will deteriorate. For example, chemotherapy was reported to induce the loss of *Clostridium* XIVa in the gut (7). *Clostridium* XIVa physiologically maintains intestinal permeability by increasing the gut concentration of polyamine (85), a substance antagonizing LPS-induced intestinal dysfunction (86). In addition, both *Bifidobacterium* and *Lactobacillus* have been reported to be able to promote the expression of genes encoding tight junction proteins, such as occludin (87) and claudin (88). The intestinal proportions of such bacteria are always decreased after chemotherapy (41), enabling increases in epithelial permeability.

Chemotherapy- or radiotherapy-related intestinal microbial dysbiosis leads to breakdown of the mucus layer

Chemotherapy- or radiotherapy-related intestinal microbial dysbiosis could disrupt the mucus layer due to the decreased proportions of butyrate-producing bacteria (42, 50, 51), such as *Roseburia*, *Coprococcus*, and *Faecalibacterium* (89). In addition, the mucus layer could be directly destroyed by several bacteria; *Citrobacter,* which increases in the gut after chemotherapy (50), secretes mucinases and glycosidases, which corrode the mucus layer (90). Furthermore, chemotherapy increases the proportion of *Enterobacteriaceae* in the gut, which impairs the host's capacity to absorb cysteine, proline, and methionine from the diet (50), resulting in a reduction in the synthesis of mucin (91).

As mentioned above, sIgA is present in the mucus layer. However, the gut concentrations of sIgA may be decreased after radiotherapy because of intestinal microbial dysbiosis. For example, the increased proportion of *Sutterella* in the gut is a feature of radiation-related intestinal microbial dysbiosis (45). To investigate the relation between *Sutterella* and gut concentrations of sIgA, Moon et al. (92) observed that, when adding *Sutterella* into the culture system of intestinal epithelial cells in vitro, sIgA concentrations would be inadequate in the apical side of cells because *Sutterella* could degrade the bound secretory component, the cleaved form of the polymeric Ig receptor (pIgR). The bound secretory components on the intestinal epithelial cells assist in transporting the dimeric form of sIgA from the basolateral to the apical side of the epithelium and further prevent sIgA from being degraded by bacterial proteases (93). In an animal model, it was found that infection with *Sutterella* resulted in an sIgA-low phenotype, which could be inherited by the offspring (92). Moreover, the sIgA-low phenotype enabled the hosts to be predisposed to dextran sulfate sodium–induced colitis, suggesting the importance of *Sutterella* in decreasing gut sIgA concentrations (92).

Therapeutic Potential of n–3 PUFAs for Chemotherapy- or Radiotherapy-Related Intestinal Microbial Dysbiosis

Biosynthesis of n–3 PUFAs

The molecular structure of PUFAs contains no less than 18 carbon atoms, and there are $\geq$2 pairs of double bonds between the carbon atoms. According to the position of the first double bond, PUFAs can be divided into n–3 and n–6 FAs. Among these, linolenic acid (18:3n–3) and linoleic acid (18:2n–6) are the shortest n–3 and n–6 PUFAs, and they also serve as precursors of other n–3 and n–6 PUFAs (94). Linolenic acid can be converted into EPA (20:5n–3) (95), and after elongating and desaturating, EPA is finally converted into DHA (22:6n–3) using β-oxidation (95). EPA and DHA are referred to as the n–3 PUFAs (96). Linoleic acid, however, can be converted into eicosatetraenoic acid, which is an n–6 PUFA (97). Accumulating evidence has suggested that the n–3 PUFAs play a critical role in attenuating inflammation (98), whereas n–6 PUFAs are associated with proinflammatory responses due to their contribution to the biosynthesis of prostaglandin E2 (99). Moreover, n–3 PUFAs have been shown to exert antagonistic effects on intestinal microbial dysbiosis, resulting in an upregulated proportion of beneficial bacteria instead of harmful bacteria in the gut (**Table 2**).Therefore, n–3 PUFAs are candidates for managing chemotherapy- or radiotherapy-related intestinal microbial dysbiosis.

n–3 PUFAs and increased beneficial bacteria

n–3 PUFAs can increase the gut proportions of beneficial bacteria (Figure 4). For example, Caesar et al. (71) found that mice fed fish-oil diets exhibited higher proportions of *Lactobacillus* and *Akkermansia muciniphila* in the gut than those fed lard. However, serum concentrations of LPS and bacterial DNA were obviously elevated along with high amounts of circulating proinflammatory cells after the lard intervention, reflecting the potential of fish oil to attenuate inflammation (71). To evaluate the anti-inflammatory effects of n–3 PUFAs rather than n–6 PUFAs in fish oil, Ghosh et al. (102) compared the severity of *Citrobacter rodentium*–induced colitis between mice fed diets with n–3 PUFAs or n–6 PUFAs for 5 wk. Relevant results showed that the mice fed the diets containing n–3 PUFAs exhibited more *Lactobacillus* and *Bifidobacterium* in the feces along with less gut inflammation than the mice fed diets containing n–6 PUFAs (102). *Lactobacillus* has been reported to be capable of suppressing the activation of the NF-κB signaling pathway by intracellularly stabilizing IκB (103), leading to downregulation of the expression of the genes encoding TNF-α and IL-8 and upregulation of *IL10* expression within enterocytes (104). In addition, *Lactobacillus* could strengthen the phagotrophic function of macrophages (105), and

TABLE 2 Clinical and preclinical studies associated with n–3 PUFAs affecting microbiota constitution[1]

Study, year (ref)	Participants/*n*	Dietary supplement/duration	Techniques	Samples	Main findings
Watson et al., 2017 (19)	Healthy volunteers/20	4 g mixed DHA/EPA (1:1)/d for 8 wk	NGS	Feces	• Bacterial family: *Clostridiaceae* ↑, *Sutterellaceae* ↑, *Akkermansiaceae* ↑ • Bacterial genus: *Coprococcus* ↓, *Faecalibacterium* ↓, *Bifidobacterium* ↑, *Oscillospira* ↑, *Lachnospira* ↑, *Roseburia* ↑
Menni et al., 2017 (73)	Female volunteers/876	Estimated food intake of n–3 PUFAs were obtained from FFQs	NGS	Blood and feces	• 350 mg DNA/d led to a serum DHA concentration of 0.14 mmol/L • Microbiome α diversity ↑ • Bacterial family: *Lachnospiraceae* family ↑, *Ruminococcaceae* family ↑
Noriega et al., 2016 (72)	A healthy volunteer	600 mg n–3 PUFAs (fish-protein diet)/d for 2 wk	NGS	Feces	• Bacterial phylum: *Bacteroidetes* ↓, *Actinobacteria* ↓, *Firmicutes* ↑ • Bacterial genus: *Faecalibacterium* ↓, *Blautia* ↑, *Roseburia* ↑, *Coprococcus* ↑, *Ruminococcus* ↑, *Subdoligranulum* ↑
Balfego et al., 2016 (100)	Patients with type 2 diabetes/35	3.0 g EPA and DHA from sardines for 5 d/wk for 6 mo	qPCR	Blood and feces	• Bacterial phylum: *Firmicutes* ↓, *Firmicutes* vs. *Bacteroidetes* ratio ↓ • Bacterial genus: *Bacteroides-Prevotella* ↑
Caesar et al., 2015 (71)	C57BL/6 mice	Experimental arm: diets enriched with menhaden fish oil for 11 wk; control arm: diets enriched with lard for 11 wk	454 pyrosequencing	Feces	• Bacterial phylum: *Actinobacteria* ↑, *Verrucomicrobia* ↑ • Bacterial class: *Alphaproteobacteria* ↑, *Deltaproteobacteria* ↑ • Bacterial genus: *Bifidobacterium* ↑, *Adlercreutzia* ↑, *Lactobacillus* ↑, *Streptococcus* ↑ • Bacterial species: *Akkermansia muciniphila* ↑
Kaliannan et al., 2015 (18)	*Fat1*$^{+/-}$ mice	Diet enriched with n–6 PUFAs (10% corn oil) or n–3 PUFAs (5% corn oil and 5% fish oil) for 8 mo	qPCR	Feces	• Intestinal tissue n–6:n–3 PUFA ratio ↓ Low n-6:n-3 PUFA ratio led to: • LPS-suppressing and/or anti-inflammatory bacteria: *Bifidobacterium* ↑, *Akkermansia muciniphila* ↑, *Clostridium* clusters IV and XIVa ↑, *Enterococcus faecium* ↑, *Lactobacillus gasseri* ↑ • LPS-producing and/or proinflammatory bacteria: *Proteobacteria* ↓, *Enterobacteriaceae* ↓, *Escherichia coli* ↓ *gamma-* and *delta-proteobacteria* ↓, *Prevotella* ↓, *Fusobacterium* ↓, *Clostridium* cluster XI ↓, segmented filamentous bacteria ↓
Yu et al., 2014 (101)	Imprinting control region mice	Control arm: natural saline for 15 d; low-dose arm: fish oil (5 mg/kg) for 15 d; high-dose arm: fish oil (10 mg/kg) for 15 d (fish oil contained 40% EPA and 27% DHA)	PCR	Feces	• Bacterial genus: *Helicobacter* ↓, uncultured bacterium clone, *WD2_aaf07d12* (GenBank: EU511712.1) ↓, *Clostridiales bacterium* ↓, *Sphingomonadales bacterium* ↓, *Pseudomonas* ↓, *Firmicutes bacterium* ↑

[1] *Fat1*, FAT atypical cadherin 1; NGS, Next Generation Sequencing; ref, reference; ↓, decreased; ↑, increased.

Bifidobacterium was found to help maintain intestinal barrier function by inhibiting LPS-induced autophagy among enterocytes (106). In addition, *Bifidobacterium* could alleviate intestinal inflammation by decreasing IL-8 secretion from enterocytes (107) and increasing the amount of T-regulatory cells at injured sites (108). Moreover, treatment with n–3 PUFAs could increase the gut proportion of *A. muciniphila* (71), which induces Paneth cells to produce mucins and the antimicrobial peptide, the regenerating islet derived protein 3γ (Reg 3γ) (109).

As mentioned above, the proportions of butyrate-producing bacteria in the gut are commonly decreased after chemotherapy or radiotherapy (42, 50). Recent evidence suggests that the intake of n–3 PUFAs could increase the relative abundance of butyrate-producing bacteria in feces, such as *Roseburia*, *Coprococcus*, *Allobaculum*, and *Butyrivibrio* (72–75). In addition to its contributions to the formation of the mucus layer, butyrate also has anti-inflammatory functions (110). First, butyrate is able to inhibit NF-κB translocation into the nucleus by suppressing

IκB degradation (111), resulting in high endogenous concentrations of IL-10 and low concentrations of IL-2 (112). Second, butyrate exclusively activates PPAR-γ, a nuclear receptor that antagonizes the expression of the gene encoding iNOS (113), and a decline in iNOS has been shown to hamper the production of nitrate by intestinal epithelial cells (114). Nitrate functions as a respiratory electron acceptor, which is essential for the reproduction of some pathogenic bacteria, such as *Escherichia* and *Salmonella* (114). When lacking nitrate, the gut proportions of these pathogenic bacteria decrease (77). Therefore, the high production of butyrate after an intervention with n–3 PUFAs can attenuate intestinal inflammation.

n–3 PUFAs and decreased harmful bacteria

As mentioned above, the typical feature of chemotherapy- or radiotherapy-related intestinal microbial dysbiosis is the increased gut proportions of harmful bacteria, such as LPS-producing bacteria and mucolytic bacteria (42, 50). Although *E. coli* and *Desulfovibrio* are capable of producing LPS (115), an animal study confirmed that *Desulfovibrio* infection also promoted the conversion of sulfates into sulfides (116), the latter of which corrupted the mucosal layer and resulted in ulcerative lesions (116). Likewise, the mucosal-adherent members of the *Bacteroides* include mucolytic species, and these mucolytic species can also impair the mucus layer (117). Recent evidence has confirmed that treatment with n–3 PUFAs could reduce the proportions of *Desulfovibrio*, *E. coli*, and the mucolytic species of *Bacteroides* (74, 76, 118) in the gut. Functionally, n–3 PUFAs have been reported to be capable of promoting the synthesis of intestinal alkaline phosphatase (IAP) (18), which could detoxify LPS through dephosphorylation (119). Moreover, n–3 PUFAs assisted in increasing the fluidity of the biomembrane by excluding cholesterol from the phospholipid layer (120), facilitating the bioactivity of IAP (121). Therefore, n–3 PUFAs can reduce the mucosal damage associated with intestinal microbial dysbiosis (Figure 4).

n–3 PUFAs and reduced inflammation

Intestinal microbial dysbiosis provokes inflammation within the gut after chemotherapy or radiotherapy. Nevertheless, recent studies have suggested that n–3 PUFAs could reduce the proinflammatory responses toward intestinal microbial dysbiosis (122). Functionally, n–3 PUFAs could directly block the signal transduction from TLR4 but not from its downstream molecules, such as MyD88 (**Figure 5**) (123). In this context, activation of the NF-κB signaling pathway was inhibited, thus resulting in decreased secretions of IL-1β, IL-6, and TNF-α (124–126). Apart from this action, DHA was shown to be capable of suppressing the bioactivity of the IκB kinase (IKK) complex by inhibiting its phosphorylation (Figure 5) (127). Meanwhile, IκB is a molecule that binds with NF-κB to block the translocation of NF-κB into the nucleus for subsequent activation of downstream gene expression (56). In this context, IκB is unable to be phosphorylated and is subsequently degraded by ubiquitination, resulting in the cytoplasmic accumulation of IκB (127). On this basis, transcriptional activation of NF-κB target genes was prohibited (56). Similarly, EPA and DHA could activate PPAR-γ (Figure 5) (128), which can antagonize the expression of NF-κB target genes by inhibiting the formation of the transcriptional complex of NF-κB (129), thus resulting in reduced inflammation.

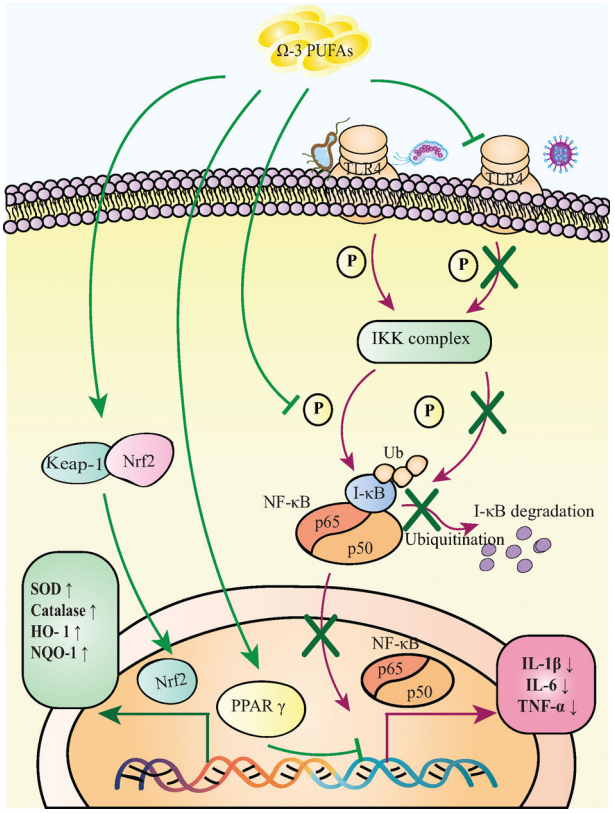

FIGURE 5 n–3 PUFAs attenuate inflammation and oxidative stress. Herein, n–3 PUFAs directly interact with TLR4, IKK, and PPAR-γ to inhibit the activation of NF-κB. As a result, secretions of IL-1β, IL-6, and TNF-α by stressed cells are inhibited. In addition, n–3 PUFAs can induce Nrf2 to dissociate from Keap1 to initiate the expressions of antioxidative genes encoding SOD, HO-1, and NQO-1. HO-1, heme-oxygenase 1; IKK, inhibitor of κB kinase; I-κB, inhibitor of κB; Keap1, Kelch-like ECH–associated protein 1; NQO-1, NAD(P)H-quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2 p45-related factor 2; P, phosphorylation; SOD, superoxide dismutase; TLR4, Toll-like receptor 4; Ub, ubiquitination; ↑, increase; ↓, decrease.

n–3 PUFAs and reduced oxidative stress

Intestinal inflammation and oxidative stress enable aggravation of tissue damage (130). Oxidative stress could induce the activation of the nuclear factor erythroid 2 p45–related factor 2 (Nrf2) signaling pathway to protect cells against oxidative damage (131). DHA was reported to be capable of switching on the Nrf2 signaling pathway to reduce oxidative stress, lessening the extent of tissue damage, because DHA and its derivative enabled Nrf2 to dissociate from Kelch-like ECH–associated protein 1 (Keap1) as a result of oxidative stress

(132). Then, the free form of Nrf2 bound with the antioxidant response element within the nucleus, targeting the expression of genes encoding superoxide dismutase (SOD), catalase, heme-oxygenase 1, and NAD(P)H-quinone oxidoreductase 1 (133, 134). In the gut, different bacteria exhibited different tolerances to oxidative stress (135, 136), and the reduced extent of oxidative stress provided optimal conditions for the reproduction of beneficial bacteria (135). By contrast, oxidative stress favored the preservation of some harmful bacteria, such as *E. coli* and *Enterococcus*, because their OxyR proteins functioned as defenders against the oxidative burst by host macrophages after being engulfed (136). However, the antioxidant system in beneficial bacteria including most species of *Lactobacillus* was not as potent as the OxyR of *E. coli* in clearing ROS (135). Moreover, several species of *Lactobacillus* even lacked SOD (135). Therefore, using n–3 PUFAs to attenuate oxidative stress will allow for the maintenance of the proper proportions of some beneficial bacteria in the gut (Figure 5).

Anticancer Effect of n–3 PUFAs

Clinically, patients undergoing chemotherapy or radiotherapy always have solid tumors. Herein, the long-standing inflammation within a tumor bed potentially has negative impacts on tumor remission after chemotherapy or radiotherapy, partially due to the infiltration of some cancer-facilitating cells such as M2 macrophages and IL-17A–producing cells (137, 138). More recently, the evidence reported by Wong et al. (139) showed that oral administration of feces from patients with colorectal cancer (CRC) either to conventional mice or to germ-free mice promoted intestinal carcinogenesis due to the increased amount of Th17 cells within the gut tissue. Gut microbes can play a critical role in inflammation and other pathological processes. Nevertheless, the anti-inflammatory and antioxidative effects of n–3 PUFAs have been confirmed. Moreover, by crossing adenomatosis polyposis coli $(Apc)^{min/+}$ mice with FAT atypical cadherin 1 (*Fat1*) mice, Han et al. (140) found that n–3 PUFAs could delay the formation of intestinal polyposis among the offspring. Likewise, previous basic studies also validated the anticancer effects of n–3 PUFAs by using immunodeficient mice bearing subcutaneous xenografts of HCT-116 and HT-29 cells (141, 142). Several clinical trials have been undertaken to evaluate the potential of n–3 PUFAs to reduce CRC risks in humans (**Table 3**).

To show the anticancerous effect of n–3 PUFAs, the following mechanism is proposed. Activation of the Wnt/β-catenin signaling pathway drives the proliferation of CRC cells (147). n–3 PUFAs could distinctly reduce the synthesis of prostaglandin E2 (148), which has been reported to be capable of activating the Wnt/β-catenin signaling pathway by cross-talking with the protein kinase (PK) family members, including PKA, PKB, and PKC (149–151). With the addition of n–3 PUFAs, prostaglandin E2–induced proliferation among intestinal stem cells is controlled. In addition to reducing the synthesis of prostaglandin E2, EPA was reported to be the substrate of cyclo-oxygenase 2 (COX-2), which catalyzes EPA into prostaglandin E3 (152). Prostaglandin E3 acts as a counterpart of prostaglandin E2, thus limiting the proliferation among intestinal stem cells (153). In another study, the C57BL/6J mice bearing azoxymethane-dextran sulfate sodium–induced CRC exhibited high abundances of *Lactobacillus* in their gut after receiving EPA treatment, with accompanying reduced sizes of colorectal tumors, decreased amounts of proliferative cells, and increased amounts of apoptotic cells within the tumors (154). However, the mechanisms underlying the anticancerous effects of beneficial bacteria on CRC deserve further investigation.

n–3 PUFA Administration and Safety

According to recommendations from the Dietary Guidelines Advisory Committee in 2015, although no upper limit was given for dietary fat intake, SFAs should be replaced by PUFAs, suggesting the importance of PUFAs for human health. To date, the US FDA has approved several fish-oil health products. For preventing coronary artery disease, the recommended daily intake of fish oil for a heathy individual is 1 g, which contains ~200–800 mg EPA + DHA (155). However, the most suitable dose for cancer patients remains to be determined, although daily doses of EPA + DHA ranging from 1.0 g to ~7.0 g were found to be safe among patients with CRC (20). However, n–3 PUFAs are easily oxidized due to the presence of 6 double bonds, which makes these compounds susceptible to oxygen free radical attack (156). As a result, n–3 PUFAs are converted into malondialdehyde (MDA) and 4-oxo-2-nonenal (4-OHE) (156, 157). Thus, MDA is a biomarker reflecting the oxidation of n–3 PUFAs in vivo, and urinary MDA concentration is commonly tested after the intake of n–3 PUFAs (157). Recently, GC-MS was applied to quantify the concentrations of n–3 PUFAs in blood samples (158). In addition, DHA concentrations in erythrocytes or in plasma were found to predict organ DHA concentrations (159). Importantly, 4-OHE was determined to induce gene mutations by forming 4-OHE–DNA adducts (160). A recent study found that fecal extracts from rats fed n–3 PUFAs plus dietary oxidants exhibited higher intestinal toxicities than those supplemented with dietary oxidants alone (157). Hence, diet should be controlled in cancer patients receiving n–3 PUFAs. Red meat should be avoided because heme iron and myoglobin are able to oxidize n–3 PUFAs (157). Optimally, food containing high quantities of vitamin E, vitamin C, polyphenols, tocopherols, and carotenoids should be considered (161). In case of infection, fish oil should be avoided, because a previous study showed that fish oil could cause sepsis by impairing LPS dephosphorylation activity (102).

Conclusions

n–3 PUFAs could be capable of reverting chemotherapy- or radiotherapy-related intestinal microbial dysbiosis, attenuating intestinal inflammation and reducing oxidative stress in the gut. Therefore, administering n–3 PUFAs should be an option in these patients.

TABLE 3 Potential therapeutic uses of dietary n–3 PUFAs in patients with cancer[1]

Study, year (ref)	Patients/*n*	Anticancer therapy	Dietary supplement/duration	Main findings
Ma et al., 2015 (143)	Gastric and colorectal cancer patients/99	Surgery	Experimental arm: 80∼140 mg n–3 PUFAs/kg in intravenous fat emulsion/d for 8 d; control arm: soybean oil and medium-chain TGs in a lipid emulsion for 8 d	• Improved lipid metabolism: FFAs ↓, TGs ↓, HDL ↑ • Attenuated inflammation: serum IL-6 ↓, serum C-reactive protein ↓, serum TNF-α ↓, serum procalcitonin ↓
Faber et al., 2013 (144)	Cancer patients/38	Radiotherapy	3.6 g mixed DHA:EPA (1:2)/d for 7 d	• EPA and DHA in white blood cells ↑, serum PGE2 concentrations ↓
Murff et al., 2012 (145)	Polyp-free control subjects/3166 Adenomatous polyp patients/1597 Hyperplastic polyp patients/544	—	Dietary PUFA intake was calculated from FFQs	• Adequate intakes of n–3 PUFAs led to: production of PGE2 in women ↓, risk of colorectal adenomas in women ↓ • Excessive intakes of α-linolenic acid led to: risk of hyperplastic polyps in men ↑
West et al., 2010 (146)	Familial adenomatous polyposis/55	Surgery	2 g EPA-FFAs/d for 6 mo	• Polyp number ↓. sum of polyp diameters ↓, mucosal EPA concentrations ↑

[1] PGE2, prostaglandin E2; ref, reference; ↓, decreased; ↑, increased.

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