ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2019 January 14; 25(2): 151-281

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Report® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

EDITORIAL OFFICE
Ze-Mao Gong, Director

PUBLICATION DATE
January 14, 2019

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World J Gastroenterol 2019 January 14; 25(2): 151-162

DOI: 10.3748/wjg.v25.i2.151

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Role of diet and gut microbiota on colorectal cancer immunomodulation

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Author contributions: De Almeida CV, de Camargo MR and Russo E prepared the manuscript; Amedei A provided overall guidance and supervision in writing the article.

Supported by "The Programma Attuativo Regionale (Toscana)" funded by FAS (now FSC) - MICpROBIMM, the Italian Ministry of University and Research (MIUR); and the Foundation 'Ente Cassa di Risparmio di Firenze'.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Manuscript source: Invited manuscript

Received: November 3, 2018

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Abstract

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers, and it is characterized by genetic and epigenetic alterations, as well as by inflammatory cell infiltration among malignant and stromal cells. However, this dynamic infiltration can be influenced by the microenvironment to promote tumor proliferation, survival and metastasis or cancer inhibition. In particular, the cancer microenvironment metabolites can regulate the inflammatory cells to induce a chronic inflammatory response that can be a predisposing condition for CRC retention. In addition, some nutritional components might contribute to a chronic inflammatory condition by regulating various immune and inflammatory pathways. Besides that, diet strongly modulates the gut microbiota composition, which has a key role in maintaining gut homeostasis and is associated with the modulation of host inflammatory and immune responses. Therefore, diet has a fundamental role in CRC initiation, progression and prevention. In particular, functional foods such as probiotics, prebiotics and symbiotics can have a potentially positive effect on health beyond basic nutrition and have anti-inflammatory effects. In this review, we discuss the influence of diet on gut microbiota composition, focusing on its role on gut inflammation and immunity. Finally, we describe the potential benefits of using probiotics and prebiotics to modulate the host inflammatory response, as well as its application in CRC prevention and treatment.

Peer-review started: November 5, 2018
First decision: December 12, 2018
Revised: December 20, 2018
Accepted: December 27, 2018
Article in press: December 28, 2018
Published online: January 14, 2019

Key words: Colorectal cancer; Diet; Inflammation; Immune response; Gut microbiota

Core tip: The host immune system plays a central role in colorectal cancer prevention and development. However, the immune response is deeply influenced by gut microbiota composition, which in turn is modulated by host diet. Therefore, diet could be used as a strong ally to prevent colorectal cancer and to support its treatment.

Citation: De Almeida CV, de Camargo MR, Russo E, Amedei A. Role of diet and gut microbiota on colorectal cancer immunomodulation. *World J Gastroenterol* 2019; 25(2): 151-162
URL: https://www.wjgnet.com/1007-9327/full/v25/i2/151.htm
DOI: https://dx.doi.org/10.3748/wjg.v25.i2.151

INTRODUCTION

Inflammation consists of an innate system with cellular and humoral responses to an injury induced by foreign organisms, dead cells or physical irritants. The aim is to attempt to inactivate the primary triggers and to regenerate the injured tissues. As a response to those injuries, a multifactorial network of chemical signals initiates and amplifies the recruitment of leukocytes (neutrophils, monocytes, and eosinophils) to the damage sites[1]. Nevertheless, when unregulated, the inflammatory process can become chronic with a persistent production of growth factors, reactive oxygen (RO) and nitrogen species (NS) that interact with DNA. As result, permanent genomic alterations have been identified[2] that can lead to the development of diseases, such as obesity[3], diabetes[4], and different cancers[5,6].

Inflammation has been considered a predisposing condition for tumor development since 1863[7,8], and nowadays at least 20% of all cancers are considered to be a direct consequence of a chronic inflammatory process[9]. Besides that, many aspects of malignancy are affected by cancer-associated inflammation[10-12]. Chronic inflammation persistently promotes a pro-tumorigenic microenvironment, which is rich in cytokines, the primary players regulators of crosstalk between malignant cells and surrounding stromal cells[13].

Chronic inflammatory intestinal disorders, such as inflammatory bowel diseases (commonly known as IBD), including Crohn's disease and ulcerative colitis, are considered to be risk factors for colorectal cancer (CRC), as their initiation and progression are closely linked to the gene-environment and gene-gene interactions[14-17]. In this scenario, the inflammatory microenvironment is considered a crucial contributing factor to the development of CRC[5,10,18,19]. Even being one of the most studied human malignancies, CRC is still the third most common cancer worldwide with 140,250 new cases estimated in 2018[20]. CRC occurs more frequently in high-income countries[21] mostly in sporadic forms, with only 25% of the cases having a familial feature[22]. Furthermore, the immune system also plays an important role in antitumor resistance[23].

Since some nutritional components, such as saturated fats, refined carbohydrates, and red meat, may have pro-inflammatory properties, the World Cancer Research Foundation and the American Institute for Cancer Research consider diet to be one of the most important exogenous factors in CRC etiology[24-28]. In addition, epidemiological studies have demonstrated that diet-gene interactions can cause diverse somatic alterations known to be involved in gastrointestinal cancer development. These distinct alterations could be associated with the wide variation of CRC risk and progression, among different individuals[29]. Besides that, food and nutritional aspects have a major impact on the modulation of host gut microbiota (GM)[30-32], which in turn have a crucial symbiotic relationship with the host by regulating its physiology and immune system, making them important factors in health and disease.

In this review, we point out the main aspects of the CRC immunological scenario and the dietary impact on CRC-associated inflammation and GM modulation. Finally, we discuss the potential beneficial effects of probiotics and prebiotics to restore intestinal microbiota in CRC prevention and as a support to current anti-CRC treatments.

IMPACT OF DIETARY HABITS AND LIFESTYLE IN CRC

Nowadays, it is estimated that 30%-40% of different cancers are caused by food, nutrition and other lifestyle factors, which make cancer a somewhat preventable disease. Overwhelming epidemiological data suggest that dietary factors, particularly those that result in overweight and obesity, influence risk, morbidity and mortality in multiple cancers[33], especially CRC[29]. Because of this, the Department of Health and Human Services at the National Institutes of Health and The Agency for Healthcare Research and Quality have attempted to implement lifestyle interventions among the population, aiming to highlight the importance of diet and healthy lifestyle for disease prevention, including cancer[34,35].

Although diet is considered an important source for mutagenic compounds (that may lead to tumor development)[36], distinct from other environmental factors such as ultraviolet (commonly known as UV) rays in melanoma (of which the role is cancer is well established), the association between diet and cancer might not be linear (Table 1). The link between nutrition and cancer can be muddled by other health-compromising factors such as smoking and alcohol consumption, sedentary lifestyle and exposure to environmental toxicants, all of which are well established risk factors for cancer development[37]. Thus, even if it is hard to 'isolate' dietary risk factors in epidemiological studies, animal models have irrefutably demonstrated the nutrition influences on cancer evolution[38]. Besides that, as demonstrated in Figure 1, diet components could act on cancer initiation and progression indirectly by increasing endocrine factor production, changing inflammatory and immunological parameters, or by changing the GM composition[37].

Direct effects of dietary components on cancer development could be represented by the strong correlation between CRC incidence and excessive consumption of fats and proteins (mainly of animal sources), processed meat, and substantial alcohol consumption (more than 30 g/d)[39-41]. People are more susceptible to develop CRC when they have an increased intake of heterocyclic amines. The main heterocyclic amines generated are 2-amino-1-methyl-6- phenyl-imidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and benzo[a]pyrene (Bap) a polycyclic aromatic hydrocarbon, the first reported group of chemical carcinogens for human cells[42]. In contrast, a vegetarian diet seems to prevent cardiovascular diseases, type 2 diabetes and cancer[43], since fruits and vegetables contain antioxidants, which scavenge free radicals and prevent DNA damage[44]. Vegetarian di*et al*so includes a variety of nutrients associated with reduced cancer risk[45]. These compounds can protect cells by affecting the bio-transformation/detoxification pathways (phases I and II), the cell signaling and endogenous antioxidant system[46]. Some micronutrients, such as zinc[47] and selenium[48], have been extensively studied and seem to have important roles in cancer prevention, whereas complex compounds such as carotenoids[49], flavonoids[50], curcumin and silymarin[51], resveratrol[52], folate[53] and total oligomeric flavonoids[54] show both direct activity against tumor cells and *in vitro* immunomodulatory effects.

In addition, nutrients such as glucose and amino acids increase tumor cell proliferation by activating growth signaling proto-oncogenes such as IGF1R, PI3K, and AKT. In this way, deprivation of nutrients and nutrient-responsive growth factors selectively kill high proliferative/resilient cancer cells by forcing their glycolytic asset toward an oxidative one. In fact, calorie restriction, defined as 30%-60% less of daily calorie requirement without malnutrition, is known to extend a healthy life span with anticancer effects, being particularly effective in reducing the incidence, mass, and metastasis of breast cancer (due to the profound metabolic reprogramming that builds up adaptive stress responses)[55]. Controlled fasting has also been demonstrated to be a promising adjuvant treatment in cancer therapy, mainly when associated with ketogenic diets that are low in carbohydrates and high in fats[56]. Moreover, short-term fasting exerts a beneficial impact on cancer immunosurveillance, as it induces regulatory T cell depletion, while an isocaloric diet with protein restriction has been demonstrated to induce an IRE1α-dependent unfolded protein response in cancer cells, increasing the number of cytotoxic $CD8^+$ T cells (CTLs). The presence of CTLs in the tumor environment (tumor infiltrating lymphocytes) is considered a positive outcome of cancer treatment[55,57].

Diet can also indirectly contribute to cancer initiation and progression by favoring obesity through over-nutrition and imbalanced diets. Obesity is closely linked to chronic inflammation, a significant cancer risk factor. When in a hyperplastic and hypertrophic state, adipose tissue is overloaded with a variety of pro-inflammatory immune cells, including classically activated macrophages, natural killer (commonly known as NK) cells, mast cells, neutrophils, dendritic cells (commonly known as DCs), B cells, CTL and T helpers 1 (Th1) cells[58]. These cells release pro-inflammatory factors such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin 1β

Table 1 Summary of the main references that suggest that diet is harmful or protective to host health

Pathways	Ref.	
	Harmful	Protective
High ratio saturated fat	[27,34,39,40]	
Obesity and cancer	[3,32,34,40,63]	
Meat intake	[29,39,41-44,123,124]	[32,45]
Alcohol intake	[41]	
Carbohydrate intake	[25,28,58]	[26,73]
Host microbiota and cancer	[65,87,100,133]	[70,72,100,105]
Probiotic and prebiotic supplementation		[69,93-96,98,99,101,102,104,106,107,110,111,116-119]

(IL-1β), and interleukin 6 (IL-6), which lead to increased local and systemic inflammation and insulin resistance[33], becoming a strong promoter of tumor progression[59].

The presence of insulin-resistant cells results in hyperinsulinemia and hyperglycemia, two important tumor-promoting effects; in fact, high concentrations of insulin, glucose, and non-esterified fatty acid (NEFA) are strong promoters of cell survival, growth, and proliferation and exert similar effects on tumor progenitors. In addition, high glucose concentrations favor glycolytic cancer cell metabolism characterized by enhanced glucose consumption[33]. Moreover, during obesity, adipose tissue macrophages, which in healthy conditions are skewed towards the M2 anti-inflammatory phenotype, are directed to pro-inflammatory M1 macrophages[60]. The M1 macrophages produce tumor-promoting cytokines (*e.g.*, TNF, IL-6, and IL-1b) and chemokines, such as Monocyte chemoattractant protein-1 (MCP-1) and Macrophage migration inhibitory factor (MIF)[61].

These data suggest that diet modulation could be used as a form of cancer chemoprevention in healthy individuals. In pharmacology, chemoprevention is used to describe the "use of pharmacological or natural agents that inhibits the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of pre-malignant cells in which such damage has already occurred"[62].

Diet is also associated with the modulation of the gut microbiome that has a significant role in host metabolism, nutrition and physiological features (intestinal epithelial cell proliferation and differentiation, pH, function) as well as with the development of the immune system and protection against pathogens[63-65]. However, in addition to diet, the GM is influenced by numerous and incompletely elucidated factors, such as host genetics, gender, age, anthropometric parameters, health/disease condition, geographic and socio-economic factors, exhibiting a huge diversity among individuals[66]. In healthy conditions, the GM plays a key role in the maintenance of the host physiological condition by modulating the host's immunity. The GM can influence neutrophil migration and function[67], as well as the differentiation of T cell subsets into Th1, Th2, and Th17 or regulatory T cells (Tregs)[68-70]. By fermenting non-digestible complex carbohydrates such as dietary fiber, these commensal bacteria can produce short-chain fatty acids (SCFAs), which can cross the intestinal epithelium and reach the *lamina propria*, directly shaping mucosal immune responses[71].

SCFAs modulate the phenotype and function of numerous immunologically relevant cells, such as colonic epithelial cells, macrophages, neutrophils and DCs[72]. Moreover, upon butyrate (one of the most produced SCFAs) stimulation, the $CD4^+$ effector T cells increase T-bet and IFN-γ expression, being able to exert either beneficial or detrimental effects on the mucosal immune system depending on its concentration and immunological milieu[73]. The presence of CTLs and IFN-γ-producing Th1 cells has been associated with prolonged survival[74,75], making some SCFAs, including butyrate, propionate, and acetate, potential therapeutic tools to modulate inflammatory responses[76,77], including for CRC treatment[78]. Nevertheless, it is important to consider that SCFAs interact with the receptor GPR43 of colonic Tregs, as well as act as histone deacetylase (HDAC) inhibitors in mucosal peripheral Tregs, which under healthy conditions, helps to maintain intestinal immune homeostasis[79-81]. However, in the tumoral scenario (*e.g.*, CRC), GPR43 can impair anti-tumor immunity, decreasing effector T cell proliferation[82].

The role of the GM in CRC progression deserves special attention because there is a strong interaction between GM, the intestinal barrier and immune cells[83-85]. For

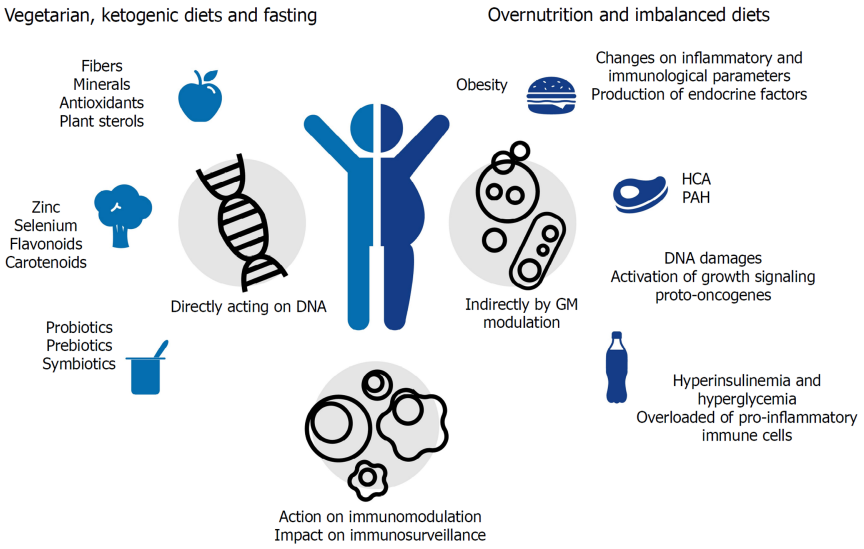

Figure 1 Diet components can directly or indirectly act on cancer prevention or initiation/progression. Beneficial direct actions are exemplified by nutrients, which can directly protect cells from DNA damage and decrease oxidative stress. A harmful direct effect is exemplified by DNA damage, activation of growth signaling proto-oncogenes and changes in proinflammatory cytokines. Indirect beneficial and harmful effects are represented by the modulation of gut microbiota and obesity induction, respectively. HCA: Heterocyclic amines; PAH: Polycyclic aromatic hydrocarbon.

example, increased epithelial permeability allows the translocation of bacteria, antigens and toxins from the lumen to the *lamina propria* into the blood stream, which may initiate both local and systemic immune responses[86]. These changes can modify inflammatory cell responses, requiring them to integrate signals (*e.g.*, cytokines) with cues such as local oxygen concentrations and other metabolites, promoting epithelial cell damage that can lead to tumor development[6].

Clinical, epidemiological and experimental data have demonstrated that nutrition and foods have a central role in cancer onset because they can change the tumor risk, the diagnosis after the onset and the life quality after treatment, in addition to their ability to ameliorate the adverse effects of chemotherapy and radiotherapy[87,88]. "Functional foods" and "nutraceuticals" are foods or food components that supply health benefits beyond basic nutrition, like peptides and proteins, amino acids, polyunsaturated fatty acids, dietary fibers, oligosaccharides, vitamins, minerals, antioxidants, probiotics and prebiotics, oils and fatty acids, carbohydrates and fibers[89]. In particular, we have focused on the immune-modulating ability of probiotics and prebiotics, which make them a potential adjuvant therapy for anti-CRC treatments.

ADJUVANT ROLE OF PROBIOTICS AND PREBIOTICS IN CRC TREATMENTS

Probiotics are defined by the International Scientific Association for Probiotics and Prebiotics (commonly known as ISAPP) as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"[90]. They can have health-promoting effects, such as antimicrobial activities against gut pathogens, the ability to decrease blood cholesterol levels, reduce colitis and inflammation, regulate the host energy metabolism and modulate the immune system[91,92]. In the last years, the use of probiotics and prebiotics to control the onset/progression, or their application as adjuvant therapies in different diseases such as influenza[93], nonalcoholic fatty liver disease[94], pancreatitis[95], and Parkinson's disease[96] has been deeply investigated. In addition, their use is also being considered as a potential anti-cancer alternative or adjuvant therapy[97], since pro/prebiotics can improve the safety of and decrease the side effects of cancer treatment (as demonstrated in several significant clinical trials)[98-100].

In addition to the direct role on GM modulation, probiotics present direct anti-cancer effects by inactivating carcinogens or mutagens, altering cell differentiation and by inducing immunomodulatory effects[101-103]. They increase immunostimulatory activities, improving gut barrier activity by secreting anti-carcinogenic and anti-

oxidative molecules[104,105], and finally by activating mononuclear cells, lymphocytes and increasing immunoglobulin A production[106,107]. Probiotic administration also reduces the expression of certain Toll like receptors (TLRs), which increases epithelial barrier resistance[102], and activates phagocytes, which contribute to the maintenance of a vigilance state against tumor cells, especially in the early stages of progression[108].

The use of the *Lactobacillus rhamnosus* GG (LGG) strain decreased cellular proliferation and carcinogenesis, due to decreased β-catenin and Bcl-2 concentrations and increased p53 and Bax expression in rats. Moreover, this strain can reduce the levels of pro-inflammatory molecules such as COX-2 and NF-κB-p65[103]. However, the recent administration of a mix of *Bifidobacterium spp and Lactobacillus spp* (the two main strains studied as probiotics in CRC therapies)[109] induced the secretion of anti-inflammatory cytokines and up-regulation of Treg and Th2 response-related gene expression[110]. However, we, in agreement and supported by another study, hypothesize that Tregs can play protective roles prior to cancer initiation in "inflammation-prone" cancers, but after tumor establishment, the Tregs can be co-opted by tumors, assuming a pro-tumorigenic role. In this way, we think that the use of specific probiotics should be applied to prevent the early phases of CRC[111].

In CRC, probiotic administration (aiming to modulate the GM and immune response) has been proven to be a promising innovative approach to counteract CRC progression and increase chemotherapy effectiveness[112]. In an animal model, the administration of combined *Bifidobacterium longum* and *Bifidobacterium breve* improved cancer control, strongly reduced tumor development and increased the efficacy of a PD-L1 blocking antibody against cancers[113]. The administration of *Lactobacillus lactis* can reduce the concentration of hydrogen peroxide (H_2O_2) and catalase activity, decreasing tissue inflammation and colonic damage in a BALB/c mouse model. These data suggest that bacteria are capable of affecting inflammatory mediators such as cytokines[114]. However, the use of some bacterial strains as probiotics could have side effects. *Lactobacillus acidophilus* induces CXCR4 (stromal-derived factor-1 receptor) mRNA expression and reduces tumor growth by 50% in treated mice and induces CT-26 cancer cell apoptosis, showing a role in metastasis prevention; however, its administration also suppressed MHC-class I expression, which is crucial in cancer surveillance[115]. Due to the heterogeneous immunomodulatory roles of probiotics, we believe that a specific selection of bacterial strain is fundamental for probiotic effectiveness. For example, disease stage progression could be an important determining factor in the probiotic strain choice. Moreover, probiotic use in cancer patients generates concern due to the risk of infection and the transfer of antibiotic resistance. Nevertheless, randomized clinical trials have not reported a significant increase in the risk of adverse effects following probiotic supplementation compared to patients who received a placebo. Furthermore, probiotic supplementation has even been proven to be safe and beneficial in these patients[116].

As an adjuvant therapy to chemo/radiotherapy in CRC patients, some clinical assays have demonstrated that probiotics can be an efficacious treatment[117], as supplementation with *Lactobacillus rhamnosus* decreased the frequency of diarrhea, abdominal distress and dose reduction due to intestinal toxicity compared to patients who received a placebo[118]. A randomized clinical trial about the efficacy and tolerability of *Lactobacillus rhamnosus* in patients with radiation-induced diarrhea showed that patients who received probiotics had better fecal consistency and decreased bowel movements[119].

Furthermore, since diet is a crucial risk factor in CRC susceptibility[120-122], the administration of prebiotics (that favor specific changes in the composition and/or GM activity) could confer benefits upon host well-being and health[123]. Prebiotics are carbohydrates, principally oligosaccharides, including fructooligossacharides (FOS) xyloogliosaccharides (XOS), inulin, fructans, and galactogliosaccharides (GOS)[124,125]. They resist digestion in the human small intestine and reach the colon, where they become substrates to fermentation by the GM. Prebiotic administration inhibits aberrant crypt formation and SCFA production[126], reduces cecal pH[127] and has anti-carcinogenic effects on the presence of resistant starch, inulin and other oligo-fructans[128,129]. In addition, prebiotics have demonstrated anti-cancer properties by downregulating the expression levels of COX-2, iNOS, NF-kB, and gastrointestinal glutathione peroxidase by their bifidogenic effects and immunomodulatory roles. Finally, prebiotics are also able to modulate the GM by inhibiting pathogen multiplication and enhancing cell apoptosis[130-134].

Probiotics work synergistically with prebiotics (symbiotic) to exert a beneficial impact on GM and on general intestinal health, which make them a potential therapeutic strategy in CRC. *Lactobacillus* and *Bifidobacteria* combined with prebiotics, such as oligofructose and inulin, have been shown to counteract tumor progression. A pro/prebiotic cocktail of *Bifidobacterium infantum, Lactobacillus acidophilus, Bifidobacterium bifidum*, maltodextrin (LBB) and oligofructose increased intestinal ZO-

1, MUC2, TLR2 and occludin expression and reduced COX-2 and TLR4 expression in rats[102].

CONCLUSION

The manipulation of nutrients could have potential implications for both the prevention and the treatment of CRC, since it can affect a diverse range of mechanisms, such as cell signaling, apoptosis, and immune system regulation, other than the overlying influence on the gut microbiome.

Diet has a great ability to modulate the cellular responses to environmental stimuli, and a balanced nutritional regime can improve immune metabolism by enhancing the cytotoxic efficiency of $CD8^+$ tumor infiltrating lymphocytes within the tumor mass, showing a potential role in improving cancer prognosis. Furthermore, diet can modulate the GM, and since the intestinal immune system is constantly exposed to numerous xenobiotic and endobiotic metabolites (which shape mucosal immune function and inflammation), the intestinal microbiome and the local immune system maintain the balance between mucosal tolerance and inflammation. In other words, GM manipulation should be a promising treatment to improve the outcomes of CRC.

The fine mechanisms by which dietary nutrients enhance anti-cancer effects of standard anticancer therapies have not been fully elucidated yet.

However, the actual scenario of poor prognosis for many cancer patients, in addition to the severe documented adverse events of current anti-cancer therapies suggest the crucial need to find complementary treatments that have limited patient toxicity and simultaneously enhance therapy responses in cancer versus normal cells. The data discussed in this review suggest that the investigation of probiotic/prebiotic application as coadjuvant anti-cancer treatments will yield interesting results; however, it is still necessary to plan different clinical trials to confirm these very promising results in humans.

ACKNOWLEDGMENTS

The authors thank Dr. Savannah Rowane Devente and Dr. Federico Boem for their corrections of English grammar and Dr. Cesare Manni who kindly drew the figure in the paper.

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