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Review

The Inhibitory Effect of Gut Microbiota and Its Metabolites on Colorectal Cancer

Chao Chen[1] and Huajun Li[2]*

[1]*Department of Colorectal Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310000, Zhejiang Province, P.R. China*
[2]*Department of Microecology, College of Basic Medical Sciences, Dalian Medical University, Dalian, Liaoning 116044, P.R. China*

Colorectal cancer (CRC) is regarded as one of the most common and deadly forms of cancer. Gut microbiota is vital to retain and promote several functions of intestinal. Although previous researches have shown that some gut microbiota have the abilities to inhibit tumorigenesis and prevent cancer from progressing, they have not yet clearly identified associative mechanisms. This review not only concentrates on the antitumor effects of metabolites produced by gut microbiota, for example, SCFA, ferrichrome, urolithins, equol and conjugated linoleic acids, but also the molecules which constituted the bacterial cell wall have the antitumor effect in the host, including lipopolysaccharide, lipoteichoic acid, β-glucans and peptidoglycan. The aim of our review is to develop a possible therapeutic method, which use the products of gut microbiota metabolism or gut microbiota constituents to help treat or prevent colorectal cancer.

Keywords: Gut microbiota, gut microbial metabolites, bacteria components, colorectal cancer, anticancer effect

Introduction

CRC is the second leading cause of cancer-related death worldwide. There are about 700,000 people dying of CRC every year [1]. CRC is considered as one of the health care challenges, and it is related to genetic encoding and more significantly, about 70% of all CRC cases are influential by environmental aspects through a couple of years, including diets, lifestyle, metabolic syndrome and gut microecology, etc [2].

Gut microbiota consists mainly of bacteria, fungi, bacteria and viruses that populate the gut, primarily the large intestine. About 90% of gut microbiota is composed of two phyla, that is, *Firmicutes* and *Bacteroidetes*, in healthy human [3]. With the development of technology, we have a better understanding of the composition, function and metabolic characteristics of the human gut microbiota [4]. There is growing evidence that commensal bacteria of human being is the vital determinant of healthy or pathological conditions, including cancer [5]. Metagenomics and metabolomics researches stressed the double effect of the gut microbiota in tumorigenesis (either inhibit cancer or promote cancer) [6]. Gut microbiota exerts the significant effects on host by producing vitamins, metabolizing dietary compounds, inhibiting the expansion and systemic infiltration of gut pathogens [7]. Other results underline the complicacy and two-way of the association between microbiota and cancer. The progression of cancer may change the microbiota. Meanwhile, altering microbiota may influence cancer development [8]. Undoubtedly, the occurrence of CRC is also related to the function of some gut microbiota constituents whose role serves as initiator or inhibitor [9].

Although we have studied the association for many years, only a small part feature was exposed. In this essay, we will list some current results about cellular and microbial metabolism regulation in CRC, concentrating on the mechanistic association of gut microbiota metabolites and constituents with CRC prevention or treatment.

The Mechanism of Gut Microbiota against Cancer

Recently evidences from in vitro and animal model to clinical trials, as well as the use of selected gut microbiota for preventing or treating CRC, have demonstrated the antiproliferative activity. The selected gut microbiota mainly includes *Lactobacillus*, *Bifidobacterium* sp., *Enterococcus faecalis* and so on. Many studies based on human cancer cells or cell line demonstrated that gut microbiota processes the function of restraining cell proliferation or stimulating apoptosis in CRC (Table 1). In the main animal models studied from 2017 to 2019, N-methyl-N-nitrosourea (MNU), 1,2-dimethylhydrazine (DMH) and azoxymethane (AOM) were used as CRC inductor respectively. The specific gut microbiota studied in these models is shown in Table 2. In human studies conducted between 2015 and 2017, several double-blind, randomized and placebo controlled researches indicated that the addition of specific gut microbiota is effective in treating, which reduces the postoperative complications of CRC

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**Corresponding author*
Phone: +86-411-86110305
Fax: +86-411-86110305
E-mail: lhjcmu@hotmail.com

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Table 1. Potential anticancer effect of gut microbiota on CRC cells.

Probiotic strain	Cells	Result	Ref.
Lactobacillus helveticus NS8	HT-29; SW480; Caco-2	The viability of HT-29 and SW480 cells ↓	[60]
Lactobacillus paracasei IMPC2.1 *Lactobacillus rhamnosus* ATCC 53103 (L. GG)	HGC-27; DLD-1	Growth ↓ Apoptosis ↑	[29]
Lactobacillus kefri P-IF *Lactobacillus kefri* P-B1 *Kazachstaniaturicensis*, *Kazachstaniaunispora* *Kluyveromycesmarxianus*	Human multidrugresistant (MDR) myeloid leukemia (HL60/AR) cells	Apoptotic ↑	[61]
Enterococcus lactis IW5	HeLa; MCF-7; AGS; HT-29; Caco-2	Apoptosis ↑ Extrinsic IL-3 receptor pathway	[62]
Lactobacillus rhamnosus strain GG (L. GG)	HGC-27; DLD-1	Proliferation ↓	[63]

Table 2. Potential anticancer effect of gut microbiota on animal model.

Probiotic strain	Animal model	Induced colon cancer (carcinogen)	Reported effect	Ref.
Lactobacilluscasei BL23	C57BL6 mice.	AOM	Protected mice against CRC development; IL-22 cytokine ↓ Caspase-7, caspase-9, and Bik ↑	[24]
Lactobacillus helveticus NS8	C57BL/6 mice, (males, 4–5 weeks old).	AOM+ DSS	Tumour number ↓ The degree of hyperplasia ↓ NF-κB ↓ IL-10 ↑ IL-17-producing T cells ↓	[60]
Lactobacillus acidophilus *Bifidobacteriumanimalis* subsp. *lactis*	F344 rats (males)	AOM+ DSS	Colorectal carcinogenesis ↓ Enhancing antioxidative capacity ↑ Apoptosis ↑	[64]
Enterococcus faecalis strain KH2	C57BL/6 mice	AOM+ DSS	DSS-induced murine experimental Colitis ↓ colitis-associated CRC ↓	[65]
L. acidophilus B. bifidum	BALB/c mice 6 week - old	AOM	Tumor suppressor miRNAs ↑ CRC ↓	[66]

(Table 3). Although these studies have provided some positive feedback, the accurate molecular mechanisms of gut microbiota in preventing, curing, and inhibiting development of cancer are still at the beginning and need further elucidations. Through the literatures reviewed, we found that gut microbiota can not only prevent cancer but also treat cancer probably by: (1) Increasing the integrity of the epithelial barrier. (2) Promoting intestinal mucous membrane adhesion, and inhibiting pathogenic bacteria adhesion. (3) Eliminating pathogens in the intestinal barrier. (4) Producing anti-microorganism substances. (5) Modulating dendritic cells (DC), affecting the polarity of T cells, regulating the immune system and inflammation.

Table 3. Potential anticancer effect of gut microbiota on human.

Probiotic strain	Patients	Reported effect	Ref.
Enterococcus faecalis T110 *Clostridium butyricum* TO-A *Bacillus mesentericus* TO-A	75 patients: probiotic 81 patients: placebo 3-15 days before and the same day after CRC resection operation	Superficial incisional surgical site infections (SSIs) ↓ Immune responses ↑ Intestinal microbial environment ↑	[67]
Pediococcuspentosaceus 5-33:3 *Leuconostocmesenteroides* 32-77:1 *Lactobacillus paracasei* ssp. paracasei 19 *Lactobacillus plantarum* 2362	38 patients: probiotic 37 patients: placebo The intervention period lasted 15 days before surgery	GIQLI "Global score" ↑ Postcolectomy gastrointestinal function ↑	[68]
Saccharomyces boulardii	15 patients: probiotic 18 patients: conventional treatment 7 days before surgery and was interrupted on the operation day	Mucosal IL-1β, IL-10, and IL-23A mRNA levels ↓ Both pro-and anti-inflammatory cytokines ↓	[69]
Bifidobacterium lactis Bl-04 *Lactobacillus acidophilus* NCFM	8 patients: probiotic 7 patients: placebo two daily tablets before surgery	Microbial diversity ↑ Butyrate-producing bacteria ↑ CRC-associated genera ↓	[70]
Lactobacillus acidophilus NCFM *Lactobacillus rhamnosus* HN001 *Lactobacillus paracasei* LPC-37 *Bifidobacterium lactis* HN019	49 patients: probiotic 42 patients: placebo 5 days before and 14 days after surgery	Postoperative infection rates ↓	[71]

Gut Microbiota Metabolites

Short Chain Fatty Acids (SCFAs)

Fiber is an important nutrient in diet. Dietary fiber is formed from undigested food components in plant cell walls, including non-starch polysaccharides, oligosaccharides, lignin, and analogous polysaccharides. Dietary fiber is the substrate of anaerobic fermentation of gut microbiota [10]. The majority of cellulose presented in the diet are broken into SCFAs, mainly acetate, propionate and butyrate [11]. The significant mechanisms of SCFAs influencing CRC may include: anti-inflammation and anti-proliferation.

Butyrate. To date, butyrate is the most widely studied of SCFAs. Butyrate is mainly produced by *Coprococcus comes*, *Anaerostipes* spp., *Eubacteriumrectale, Faecalibacteriumprausnitzii, Roseburia* spp. [12]. Butyrate is constituted by two molecules of acetyl-CoA, yielding acetoacetyl-CoA, which is further converted to butyryl-CoA via β-hydroxybutyryl-CoA and crotonyl-CoA [13].

Butyrate provides energy for colonic cell proliferation, but it does not have the same effect on CRC cell, because the energy of CRC cells is from glucose utilization and aerobic glycolysis due to Warburg effect [14]. Therefore, butyrate can regulate gene expression epigenetically via inhibiting class I histone deacetylase (HDAC), such as HDAC1 and HDAC3 [15]. Butyrate targets Fas and p21 in animal tumor models which have proapoptotic and antiproliferative activities, respectively [16].

Butyrate also serves as the agonist for certain G protein coupled receptors (GPR), including GPR43, GPR41, GPR109A, and Olfr78 [17]. GPR promotes naive CD4+ T cells to convert into immunosuppressive Tregs and upregulate the level of anti-inflammatory cytokine IL-10 and the pro-inflammatory cytokine IL-17 when it is activated in DCs. Macia L reported the absence of GPR accelerates colonic inflammation and the development of CRC in multiple experimental model systems [18]. Butyrate exerts the anti-proliferation and pro-apoptosis effects via signaling pathways in colonic epithelial tissues. Butyrate treatment (in mM concentrations) induces *mothers against decapentaplegic homolog 3* (SMAD3) mRNA, which is a TGF-β regulatory gene and can lead to the progression of cancer, and enhances the pro-apoptotic effects of TGF-β signaling in the gut [19]. Butyrate can also lead to the fragmentation of genomic DNA, apoptosis and G1/G2 cell cycle arrest in CRC cells [20]. Butyrate actives Wnt pathway which is related to an up-regulation of the active β-catenin. β-catenin can be linked to one of two histone acetyltransferases, the cAMP-response element-binding protein (CREB) binding protein (CBP) or p300 [21]. Butyrate also influences barrier function [22]. In healthy conditions, normal gut microbiota can prevent the entry of pathogenic gut microbiota and cancerogenic material from intestinal epithelium [23]. According to some researches, SCFAs stimulate the expression of molecules which form the epithelial barrier and mucin production through activating 5' adenosine monophosphate-activated protein kinase (AMPK) and TLR4 pathway [24].

Other studies reported that butyrate may increase the susceptibility of tumorigenesis with gene modified [25].In a mouse model of adenomatous polyposis (APC) tumor suppressor gene mutation, butyrate reinforced the proliferation of colon epithelial cells and raised the number of tumors [26].

Propionate. Propionate is synthesized from phosphoenolpyruvate (PEP) via the succinate pathway or the acrylate pathway, in which propionate is produced by reducing lactate [13]. Propionate is mainly producted by *Bacteroides* spp., *Phascolarctobacteriumsuccinatutens*, *Dialister* spp., *Veillonella* spp., *Megasphaeraelsdenii*, *Coprococcuscatus, Salmonella* spp., *Roseburiainulinivorans, Ruminococcusobeum* [12]. There are evidences about the over-expression of PRMT1 in the early stage of CRC, which contributes to the malignant characteristics of the progression of CRC. A trail demonstrated that propionate can down-regulate PRMT1 in the HCT116 cell line. According to siPRMT1 treatment, the reduction of PRMT1 will induce apoptosis by inhibiting phospho-p70 S6 kinase. However, the mechanisms of the association with propionate and PRMT1 regulation are currently unknown [27]. Propionate also possesses HDAC inhibitory effect. Propionate activates GPR41 and GPR43, the host will release satiety hormones and other metabolic and induce anti-inflammatory effects [28]. It is noteworthy that propionate inhibits the cytokine-induced expression of VCAM-1 and ICAM-1 and, as a consequence, mononuclear leukocytes adhere to the endothelial cells through inhibiting the activation of NF-κB. Maybe the activity of PPARα can active the anti-inflammatory and anti-atherosclerotic activity of propionate [29].

Polyphenolic Metabolites

Polyphenols are another group of compounds found in plants. Polyphenolic metabolites have the abilities to repair damaged DNA, inhibit colon pathogens and regulate cell apoptosis [30]. Many researches indicated that the mechanism of these actions is mediated by modifying the synthesis of eicosanoids, down-regulating the inflammatory cascade, regulating DNA synthesis and inducing luminal detoxification enzymes [31]. These evidences indicate that polyphenols are beneficial to host health and prevent CRC.

Urolithins. Ellagic acid, which exerts in some berries and nuts, is a kind of polyphenol. It can be metabolized into urolithins with the activities of pro-estrogenic and anti-estrogenic by gut microbiota [32]. The anti-cancer effects of urolithins are related to multiple pathways, as it downregulates COX-2 to lower prostaglandin production, decreases the proliferation of cell and delays migration of cell and decreases activity of matrix metalloproteinas-9 (MMP-9). Mechanistic studies have suggested that urolithin A suppresses Wnt signaling and guard against cancer [33].The treatment of dietary submicromolar urolithin A has been reported to upregulate autophagy and suppress the development and metastasis of CRC SW620 cells. Subsequently, urolithin A stimulates cell death and exerts anti-metastatic effects by autophagy and caspases, which is revealed by Atg5-siRNA and Z-VAD-FMK addition. These results provided original concepts to understand the antitumor role of urolithin A in CRC [34].

Equol. Gut microbiota metabolizes soya is oflavone daidzein, a polyphenol present in soybean into equol. Equol has the effect of estrogenic; it is also a valid antagonist of dihydrotestosterone in vivo. An analysis provided gender-based data to determine that soy consumption can reduce CRC risk by roughly 21 percent in women [35]. Another research found that equol inhibit the five kinds of CRC cell proliferation by its estrogenic activities and antioxidant activities, meanwhile, only different concentrations of ERβ agonist significantly inhibited the growth of CRC cells. Estrogen receptor inhibitor and ERα agonist did not present significant on the cell proliferation of CRC cells [36].

Tryptophan Metabolites

Tryptophan metabolite arise from protein catabolism, including indole, indole-3-aldehyde, indole-3-acetic acid, and indole-3-propionic acid. Indole-3-acrylic acid is generated by *Peptostreptococcus*. in colonic lumen [37]. This metabolite activates the antioxidant machinery in cells and is also an agonist for AhR, which exerts in colonic epithelial cells and suppresses inflammation and carcinogenesis [36]. The studies mentioned above suggest that indole-3-acrylic acid has the effect of anticancer.

Conjugated Linoleic Acids (CLA)

CLA belongs to the family of isomers of linoleic acid (LA). *Lactobacillus* and *Bifidobacterium* can convert LA to CLA. The CLA has the ability to control the morbidity of skin cancer, breast cancer, prostate cancer, and CRC in rodent models [38].CLA suppresses PI3K/Akt and ERK signaling cascade, consequently induces apoptosis and suppress cancer cell lines' cell cycle [39]. In previous studies, the anti-cancer mechanism of t10, c12-CLA over expressed a new proapoptotic protein, NAG-1 through AKT/GSK3b pathway and up-regulates ATF3 expression [40]. CLA also suppresses the growth of HT-29 and Caco-2 cells in a dose-dependent manner by upregulating the PPAR-c gene and inducing apoptosis as a ligand for the PPAR-c [41].

Ferrichrome

Ferrichrome is known as a small high affinity and iron-chelating molecules siderophore, which is created by *Lactobacillus casei ATCC334*; nowadays, it is regarded as an anti-cancer molecule. Ferrichrome induces apoptosis by activating the c-Jun N-terminal kinase (JNK)-DNA damage-inducible transcript 3 (DDIT3) pathways and upregulating the cleavage of poly adenosine diphosphate-ribose polymerase (PARP) in CRC cells [42]. Ferrichrome is safe for non-cancerous cells, as the growth of IEC-18 and primary cultured cells that belong to the mouse's small intestine are not influenced by it. Additionally, it is found that ferrichrome is equal to or even better than anticancer agents, such as 5-FU and cisplatin, in anti-tumor effect against CRC cells [43]. These results indicate that ferrichrome is a practical anti-cancer drug to inhibit the progression of CRC.

Bacteriocins

Bacteriocins, which are large molecular weight antimicrobial compounds produced by *L. acidophilus*, *Bifdobacteriumbifdum NCFB 1454*, *L. plantarum*, *Lactococcus lactis,*including bacterial peptides or proteins with antimicrobial properties [44, 45].

A series of researches indicate that bacteriocins are effective against food-borne pathogen. Such as bifdocin B, which *B. bifdum NCFB 1454* secretes, protects host from several pathogenic bacteria, including *Salmonella enterica ser. typhimurium SL1344* and *E. coli C1845* [46]. *Pediococcusacidilactici* can generate Pediocin CP2. In undialys is (1,600 AU/ml) and dialysis (800 AU/ml) fractions of Pediocin CP2, the authors observed inhibition of human colon cancer cell (HT29) growth in 55 and 53.7%, respectively [47].

As one of the natural AMPs, Nisin is generated by strains of *Lactococcus lactis subsp.* According to Knychalski B, nisin can significantly reduce mean tumor volumes no matter what concentrations [48]. Another study indicates that nisin A can reduce the expression of these MMPs and carcino-embryonic antigen (CEA) in CRC cells, compared to untreated cancer cells. Nisin A suppresses the metastatic process by down regulating CEA, CEAM6, MMP2F, MMP9F genes [49]. According to Ahmadi, nisin increases the bax/bcl-2 ratio in mRNA as well as protein levels, and thus causes the apoptosis on the SW480 cancer cell lines. These results implied that nisin possesses the cytotoxic effect on CRC cells and exerts the pro-apoptosis activity through intrinsic pathways [50]. However, additional investigations are required to find the mechanism why nisin has the anti-metastatic activity.

Bacteria Components

As mentioned above, gut microbiota metabolites have anti-cancer effects, and the components of gut microbiota can also trigger anti-tumor immune response. These components exist in the cell wall of gut microbiota. Here we will talk about lipopolysaccharide (LPS), lipoteichoic acid (LTA), β-glucans, and peptidoglycan.

Lipopolysaccharide (LPS)

LPS consists of Gram-negative bacteria (*Escherichia coli* or proteus species) cell wall. Several researches showed that LPS activates the toll-like receptor 4 (TLR4) which is one of pattern recognition receptors (PRRs) and exists on the surface of the host's cell. Hence, LPS activates immune T cell-mediated response to kill cancer cells [51]. However, other results demonstrated that LPS induce tumorigenes is due to the existence of the LPS receptor on colonocytes, which can prevent the cell from dying, upregulate the cellular immune response via TLR2, and consequently, activate following proinflammatory cytokine signaling [52].

Lipoteichoic acid (LTA)

LTA is regarded as the counterpart of LPS [53]. LTA can be found in Gram-positive bacteria (*Bifidobacterium* spp. *or Lactobacilli*). NO synthase induces cell death when the body is infected with the virus. LTA activates NO synthase by secreting TNF-α, which up regulates the framework of vital phagocytes is receptors including TLRs and FcγRIII [54]. This is very significant to initiate acquired immune responses, because the primary T cells differentiate the corresponding CD4+ T helper subtypes when encountering antigens produced by APCs and the cytokines released in the acquired immunity [55].

β-Glucans

β-Glucans are biopolymers of D-glucose linked in the β- (1 → 3) position with glucose side branches (β-(1 → 6)-linkage) of various sizes. β-Glucan guards the body against cancer cells by stimulating precursor cells in the bone marrow and inducing new immunocytes releasing to different lymphatic organs. β-Glucan also activates the killer cells through affecting the surface molecules in macrophages and NK cells [56]. These beneficial properties are vital when chemotherapy and radiotherapy have broken the anti-cancer immune system [57]. In the case of neutrophils, β-Glucan helps neutrophils identify cancer cells, trigger different death mechanisms, and then increases the results of monoclonal antibodies and vaccines [58].

Peptidoglycan

Another main component of the Gram-positive bacteria cell wall is peptidoglycan (approximately 90%) [59]. Wang found that whole peptidoglycan (WPG) from the *Lactobacillus paracasei subsp. paracasei M5* strain prevents the proliferation of HT-29 cell and induces apoptosis. The apoptosis property of WPG is mediated by up regulating proapoptotic genes, down regulating antiapoptotic genes and promoting the release of Cytochrome C (Cyto C) in the mitochondria to the cytosol. Furthermore, the antiproliferative activity of WPG depends on dose [59].

Conclusion

Gut microbiota is a popular research topic these years because of their beneficial effects on human health. In this essay, we focus not merely on the antitumor functions of gut microbiota metabolites, but on the constituents of the bacterial cell wall. Gut microbiota metabolites can be classified into low molecular weight compounds like organic acids and macromolecular antibacterial compounds like bacteriocins. They have multiple effects, such as HDACi, and exhibit anti-inflammatory roles via signaling pathways, affecting barrier function, repairing damaged DNA, regulating cell apoptosis and destroying target cells. The components of the bacterial cell wall include LPS, LTA, β-glucans and peptidoglycan. The mechanisms of preventing CRC action include enhancing immune defense system and anti-proliferation of the CRC cell. In order to clear the intricate functions of gut microbiota, more studies are needed to investigate the specific mechanisms of the gut microbiota metabolites and constituents, and then find more beneficial substances associated with the gut microbiota. It is anticipated that the gut microbial metabolites will be applied in CRC treatment in the near future.

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Conflict of Interest

The authors have no financial conflicts of interest to declare.

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