

World Journal of *Clinical Cases*

World J Clin Cases 2019 November 26; 7(22): 3683-3914



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The WJCC is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for WJCC as 1.153 (5-year impact factor: N/A), ranking WJCC as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: Ji-Hong Liu

Proofing Production Department Director: Yun-Xiaojuan Wu

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Bao-Gan Peng, Sandro Vento

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2307-8960/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

November 26, 2019

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INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Colorectal cancer: The epigenetic role of microbiome

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Author contributions: Sabit H conceptualized the idea and wrote the manuscript; Cevik E made all the figures and illustrations; Tombuloglu H revised the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

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Manuscript source: Invited manuscript

Received: April 1, 2019

Peer-review started: April 1, 2019

First decision: May 30, 2019

Revised: October 23, 2019

Accepted: October 30, 2019

Article in press: October 29, 2019

Published online: November 26, 2019

P-Reviewer: Demetrashvili Z, Garg P, Ng QX

S-Editor: Dou Y

L-Editor: Filipodia

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Abstract

Colorectal cancer (CRC) is the third most common cancer in men (746000 cases per year) and the second most common cancer in women globally (614000 cases per year). The incidence rate of CRC in developed countries (737000 cases per year) is higher than that in less developed countries (624000 cases per year). CRC can arise from genetic causes such as chromosomal instability and microsatellite instability. Several etiologic factors underlie CRC including age, diet, and lifestyle. Gut microbiota represent a proven cause of the disease, where they play pivotal roles in modulating and reshaping the host epigenome. Several active microbial metabolites have been found to drive carcinogenesis, invasion, and metastasis *via* modifying both the methylation landscape along with histone structure in intestinal cells. Gut microbiota, in response to diet, can exert both beneficial and harmful functions in humans, according to the intestinal balance of number and types of these bacteria. Although the intestinal microbial community is diverse among individuals, these microbes cumulatively produce 100-fold more proteins than the human genome itself, which calls for further studies to elaborate on the complicated interaction between these microorganisms and intestinal cells. Therefore, understanding the exact role that gut microbiota play in inducing CRC will help attain reliable strategies to precisely diagnose and treat this fatal disease.

Key words: Colorectal; Cancer; Colorectal cancer; Epigenetics; Gut; Microbiota

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Core tip: Colorectal cancer is serious disease that affects males and females late in their lives. Several etiologic factors trigger colorectal cancer; however, the gut microbiome is responsible of most of the cases. Gut bacteria can produce a variety of chemical compounds that affect intestinal cells and might transform them into malignant ones. In this review, we describe the main mechanisms by which gut microbiota exert these functions.

E-Editor: Liu JH



Citation: Sabit H, Cevik E, Tombuloglu H. Colorectal cancer: The epigenetic role of microbiome. *World J Clin Cases* 2019; 7(22): 3683-3697
URL: <https://www.wjcn.net.com/2307-8960/full/v7/i22/3683.htm>
DOI: <https://dx.doi.org/10.12998/wjcc.v7.i22.3683>

INTRODUCTION

Colorectal cancer (CRC) is one of the primary causes of cancer-related deaths globally^[1]. It occurs as a result of complicated sequences involving mutation accumulation that is either genetic or epigenetic^[2]. The process of CRC carcinogenesis is a quite slow, starting with minor inflammation followed by adenomatous polyps in the epithelium, and finally adenocarcinoma^[3]. Given the crucial role of epigenetic changes in developing CRC, 95% of cases are sporadic *i.e.* appear in patients with no family history for the disease. Meanwhile, minor ratio (3%) is attributed to hereditary nonpolyposis CRC, and 2% of cases are caused by other hereditary disorders such as MYH-associated polyposis and familial adenomatous polyposis^[2,4].

Microorganisms occupy almost every part of the human body, armed with a huge number of genes, where it could interact, modulate, or disrupt a wide array of human genes especially in colonic cells^[5]. Interestingly, the human microbiome encodes for approximately 100-fold more proteins than the human genome itself. This microbiota comprise 1000 to 1500 bacterial species, and the composition of the microbiome is significantly diverse among individuals^[6]. These species belong to just a few phyla: *Firmicutes*, *Bacteroidetes* (most prevalent), *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, *Fusobacteria*, and *Cyanobacteria*^[7]. Although distribution of the microbiota in terms of types and number is common in healthy individuals, it differs significantly in diseased persons. In addition to bacteria that compose the gut microbiome, eukaryotic fungal species have recently been found to co-exist with bacterial species, the major component of the microbiome^[8].

It is well established that gut microbiota play critical roles in the progression of CRC either *via* their metabolites or interaction with their host intestinal epithelial cells^[9]. Imbalance of this microbiota has been associated with several disorders including inflammatory bowel disease and CRC^[10]. Nonetheless, several studies have related the changes in microbiota to a cause of disease, while others have indicated that these changes are merely a result; however, this issue demands further investigation^[11]. In this review, we highlight the recent studies that addresses the causal link between gut microbiota and CRC onset and progression. Meanwhile, the epigenetic changes underlying CRC and its microbial root will also be described.

CRC

CRC is one of the most prevalent malignant tumors and the third most common cause of cancer-related death worldwide^[12]. It is the third most common malignancy in males and the second in females, with a lifetime risk of about 6%^[13]. Being well-developed, CRC can metastasize -even after operation- to distant organs such as the liver and lungs, forming secondary CRC^[14]. The common risk factors underlying CRC involve genetics^[15], environmental pollution^[16], diet^[17], age^[18], alcohol consumption^[19], smoking^[20], obesity^[21], and physical inactivity^[22], with gut microbiota standing alone as a potent risk factor^[23] (Figure 1). It is well established that CRC arises due to accumulation of genetic mutations. Large studies showed that approximately 13000 mutations in 67 genes correlate with CRC. Among them, only 12 genes were found to be closely related to CRC^[24]. Different types of genomic instability predispose patients to CRC including microsatellite instability (MSI), in which frequent insertions and deletions are prevalent, and chromosomal instability (CIN), in which gain or loss of chromosomes prevail^[25]. CIN is responsible for about 85% of CRC cases, where loss of chromosomal segment/arm includes 15q11-q21, 17p12-13, and 18q12-21 and gain of chromosomal segment/arm includes 1q32, 7p, 7q, 8q, 13q, 20p, and 20q^[26,27].

Several genes are directly correlated with CRC. Examples include *APC* in which inactivation leads to triggering the Wnt signaling pathway to initiate colon polyps which can be benign (*e.g.*, hyperplastic polyp), pre-malignant (*e.g.*, tubular adenoma) or malignant (*e.g.*, colorectal adenocarcinoma)^[28]. Furthermore, transforming growth factor receptor 2 *TGFBR2* is involved in almost 30% of CRC cases. The downstream effector of this genes, *i.e.* *KRAS* was found to be activated in 55%-60% of CRC cases.

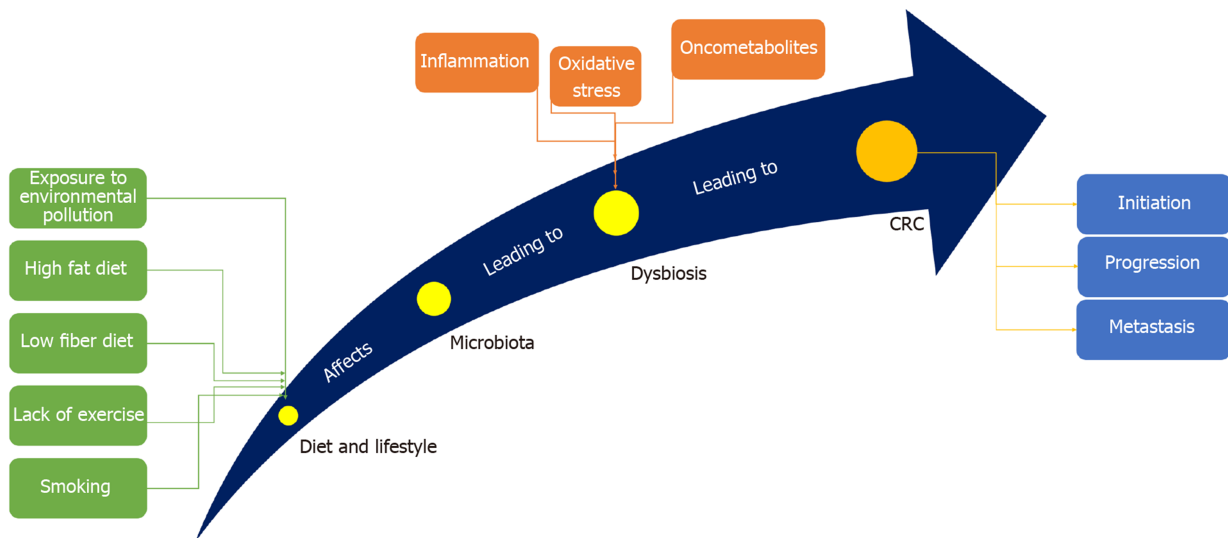


Figure 1 The way gut microbiota induces CRC. Several factors affecting the normal behavior of microbiota such as low fiber and high-fat diets. This change might affect the number/types of gut bacteria or cause them to express different kinds of proteins and metabolites. A category of these metabolites could be oncogenic (oncometabolites) and trigger inflammation in gut epithelial cells leading to cancer initiation. Bacterial metabolites also could enhance cancer spreading and metastasis. CRC: Colorectal cancer.

Mismatch repair genes such as *MLH1*, *MSH6*, *MSH2*, and *PMS2* causing frameshift mutations were found to induce MSI, triggering the development of CRC^[29] (Figure 2).

Epigenetic regulation of gene expression analysis is a validated tool to correlate gene expression changes with cancer development^[2,30]. Through the last three decades, solid common knowledge has been established to indicate that the perturbation of epigenetic mechanisms leads to cancer initiation and progression^[29,31]. Identification of CRC epigenetic changes has revealed that almost all CRCs have abnormally methylated genes. Although rare data have been provided to highlight the pattern of specific histone modifications in CRC, certain histone modifications (such as acetylation, methylation, and phosphorylation) have been found to work in harmony with DNA methylation to regulate CRC-related gene expression that is involved in cancer initiation and progression^[1,32]. Therefore, a deep understanding of epigenetic changes related to CRC pathogenesis might help develop epigenetic-based biomarkers for CRC diagnosis and prognosis, and hence, epigenetic-based therapy^[29].

GUT MICROBIOME

Function

In the normal adult person, the gut microbiota comprise approximately 10^{14} bacterial cells that live in commensalism with the host, where they substantially facilitate various aspects in the host health and disease^[33]. The normal gut microbiota are rich in anaerobic bacteria, which are 100- to 1000-times more than aerobic and facultative anaerobic bacteria, respectively^[34]. The colon has a reductive environment devoid of oxygen, which allows *Bacteroidetes* and *Firmicutes* to be the dominant phyla followed by *Actinobacteria* and *Verrucomicrobia*^[35]. For bacteria, the colon represents a suitable niche as it provides them with elevated pH, nutrients, and low concentration of bile salts and pancreatic secretions. These conditions, indeed, are favored by bacteria to flourish and proliferate^[10]. Commensal bacteria start colonization of the host during birth and continue to variate in number and type along with the host development^[36]. It is well established that our gut microbiome is responding to any dietary shift, where switching from polysaccharides-rich diets to that high in animal fat eventually leads to a hasty shift in the gut microbiome^[37]. Commonly in the gut, the prevailed microbial product is lipopolysaccharide (LPS), produced by Gram-negative bacteria, function to stimulate the innate immunity, thus, protecting against inflammation that leads to cancer^[38] (Table 1).

Protective role

Gut microbiota is crucial for numerous characteristics of host biology^[10,39]. They enable the host to digest and metabolize indigestible polysaccharides^[40]. The gut microbiota plays an important role in maintaining gut homeostasis^[41]. Furthermore, gut microbial community also participates effectively in the normal cellular proliferation. To keep

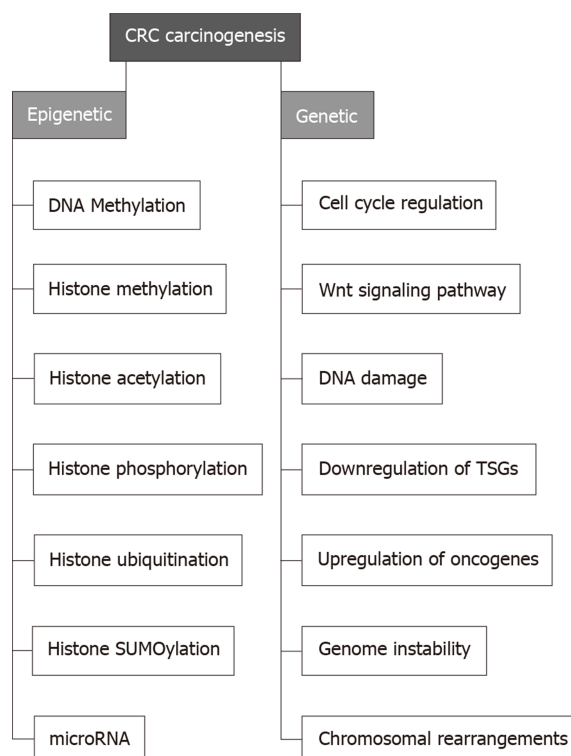


Figure 2 Different pathways through which CRC develops. CRC: Colorectal cancer.

its habitat for millions of years, several gut microbiota essentially protect the host against CRC^[42]. Reports have indicated that enterotoxigenic *Bacteroides fragilis* is capable of induce apoptosis in CRC cells^[42]. Generally, diet is metabolized by microbiota into potent oncometabolites and tumor-suppressive metabolites. Whereas, the same microbiota can digest fiber into short-chain fatty acids (SCFAs)^[43]. It is well known that SCFAs have anti-inflammatory properties and can increase the level of colonic regulatory T cells (Tregs) and protect the host against colitis^[43,44]. The most common SCFAs produced in the gut are acetate, propionate, and butyrate^[45]. Butyrate is one of the important sources of energy, where it provides the cells with 5%-15% of its caloric requirements. *Faecalibacterium prausnitzii* and *Eubacterium rectale* are the main gut bacterial species that produce butyrate^[44,46]. Butyrate controls cell proliferation, differentiation, and apoptosis among other functions in colon cells^[23,47]. It exerts also a preventive role where it ameliorates the harmful effects of N-nitroso compounds, a product that accumulates in the colon upon intake of heat-treated and processed meat^[48] (Figure 3). It has been indicated that *Clostridium* species enhances Treg cell abundance by increasing the production of potent anti-inflammatory molecules such as cytokine interleukin 10 (IL-10)^[49]. Lactic acid bacteria have also shown protective properties against CRC *via* different mechanisms that include strengthening the mucosal barrier and altering luminal secretions, resulting in underpinning of the host immune system. Ursodeoxycholic acid (UDCA, ursodiol) is a metabolic byproduct of intestinal bacteria, with a chemical structure that resembles deoxycholic acid (DCA)^[50]. While DCA promotes the initiation of CRC, UDCA function to prevent the disease. It was reported that UDCA inhibits the expression of cyclooxygenase-2 (COX-2) by Ras-dependent and RAS-independent mechanisms in CRC cells^[51]. UDCA prevents colon cells from the harmful effect of DCA *via* inhibiting the DCA-induced extracellular signal-regulated kinase and Raf-1 kinase activity and the activation of epidermal growth factor receptor (EGFR)^[52].

Pro-carcinogenic role

Microbiota-mediated carcinogenesis is a complex process that takes place through changing host cell proliferation, influencing the host cell immune system, and metabolizing dietary factors^[53]. A plethora of research has suggested that an imbalance in normal intestinal microbiota can trigger inflammatory conditions by producing carcinogenic metabolites that lead to cancer formation, and about 16% of human cancers are triggered by bacteria^[36,53]. Gut bacteria can attack intestinal epithelial cells to cause inflammation, that in turn, increase the risk of developing CRC^[54]. For CRC to occur, the microbiota-host interaction must be dysregulated,

Table 1 Gut microbiota are involved in CRC carcinogenesis

Microorganism	Role in CRC initiation/progression	Ref.
<i>Lactobacillus casei</i> BL23	Immunomodulatory effect <i>via</i> downregulation of the IL-22, and an antiproliferative effect, <i>via</i> upregulation of caspase-7 and caspase-9	[109]
<i>Escherichia coli</i> NC101	Production of colibactin that induces CRC	[110]
<i>Fusobacterium nucleatum</i>	Activation of β -catenin signaling and induction of oncogenic gene expression that promotes growth of CRC cells <i>via</i> the FadA adhesion virulence facto. It produces also the autotransporter protein, Fap2, that has been shown to potentiate the progress of CRC <i>via</i> inhibiting immune cell activity	[111]
<i>Eubacterium rectale</i>	Production of butyrate to induce IL-10, the anti-inflammatory cytokine	[112]
<i>Bacteroides fragilis</i>	Production of Enterotoxigenic <i>Bacteroides fragilis</i> (ETBF) toxin that promotes CRC by modulating the mucosal immune response and inducing epithelial cell changes. ETBF stimulates E-cadherin cleavage and facilitates cell tumor metastasis	[113]
<i>Streptococcus bovis</i>	Triggering of inflammations, bacteremia, and endocarditis, that leads ultimately to colorectal cancer	[114]
<i>Clostridium septicum</i>	Production of alpha toxin that binds GPI-anchored cell surface receptors including the human folate receptor as well as the neuronal molecules contactin and Thy-1 (CD90)	[115]
<i>Enterococcus faecalis</i>	Damaging the colonic epithelial cell DNA	[116]
<i>Bifidobacterium</i>	Production of β -galactosidases, which has antitumor activity	[117]
<i>Helicobacter pylori</i>	Induction of inflammatory responses, alteration of gut microflora and release of gastrin, which may contribute to tumor formation	[118]
<i>Faecalibacterium prausnitzii</i>	Production of butyrate to induce IL-10, the anti-inflammatory cytokine that protects against cancer formation	[119]
<i>Enterotoxigenic bacteroides</i>	Induction of early-stage carcinogenic, that might lead to early colorectal carcinogenesis	[113]
<i>Clostridium nexile</i>	Contribution to the anticancer effect of <i>Pseudomonas aeruginosa</i> . It improves also malnutrition in infants	[120]
<i>Fusobacterium varium</i>	Activate the E-cadherin/ β -catenin signaling pathway and association with epigenetic phenotype, such as microsatellite instability and hypermethylation, <i>via</i> its strong adhesive and invasive abilities resulting in malignant transformation of epithelial cells	[121]
<i>Actinomyces odontolyticus</i>	Causes colon actinomycosis only when the epithelial barrier was perished	[122]
<i>Veillonella dispar</i>	Might be able to enhance the dosage response to CRC chemotherapeutic agents or reduce the side effects of these drugs	[123]

CRC: Colorectal cancer; ETBF: Enterotoxigenic *Bacteroides fragilis*.

resulting in disruption of cellular homeostasis^[55]. The major component of the gut immune system, Peyer's patch, is robustly influenced by gut microbiota^[56]. The host diet can trigger gut microbiota to be involved in the early stages of CRC carcinogenesis^[57]. Upon metabolism of saturated fatty acid- and sugar-rich diets, gut bacteria produce harmful procarcinogenic products including polyamines hydrogen sulfide, secondary bile acids such as DCA and lithocholic acid (LCA), and reactive oxygen species (ROS), which induce chronic inflammation, and hence elevate the susceptibility of cells to develop CRC^[58]. DCA is a metabolite of the gut microbiota that induces cancer stemness by regulating the muscarinic 3 receptor/Wnt intracellular signaling pathway^[59]. It can also trigger the production of Nur77 protein, which is positively correlated with CRC when upregulated^[60]. Meanwhile, DCA induces CRC *via* downregulation of miR-199a-5p that degrades *CAC1*, the tumor

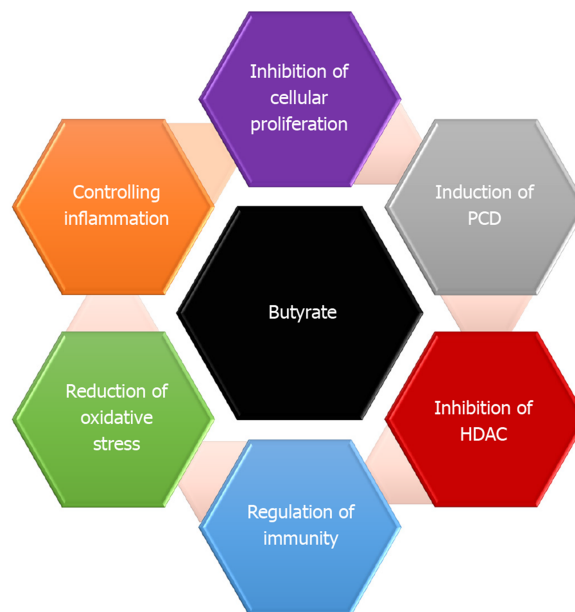


Figure 3 Different functions of butyrate in protecting against CRC. CRC: Colorectal cancer; HDAC: Histone deacetylase.

suppressor gene plays a role in CRC^[61]. LCA (aka 3 α -hydroxy-5 β -cholan-24-oic acid), a secondary bile acid synthesized by gut microbiota, is verified to a promoter of CRC^[62]. Gut bacteria produce LCA by utilizing DCA^[63]. Both LCA and DCA can enhance cancer stemness^[64]. Furthermore, LCA and DCA activate the EGFR signaling pathway, inducing DNA damage, and causing oxidative stress, apoptosis, mutation, and activation of the protein kinase C pathway^[59].

Trimethylamine (TMA) is solely synthesized by gut microbiota (in humans) from various dietary nutrients including choline and carnitine (found in red meat)^[65]. It reacts with flavin monooxygenase to produce trimethylamine-N-oxide (TMAO), a microbial metabolite involved in CRC progression^[66]. A high incidence rate of CRC was noticed in omnivorous individuals, as they produce more TMAO compared to vegans and vegetarians who show low incidence rate^[67]. The genetic pathway by which TMAO triggers CRC remains unclear.

Furthermore, specific gut bacteria such as *Enterococcus faecalis* was found to induce COX-2, that generates pro-proliferative signals through prostaglandin E(2) (PGE₂)^[68]. Several Gram-negative bacteria produce LPS that activates TLR4, COX-2, and then PGE₂, leading to inhibition of programmed cell death and increase cell proliferation^[69]. Moreover, there is an increased resistance to macrophage killing and MAPK activation in those who have the *pks* (polyketide synthase) island in *E. coli* isolated from CRC patients^[70]. Activated TLR also enhances angiogenesis through MAPK and NF- κ B signaling networks^[71] (Figure 4).

Other CRC-related bacterial metabolites were highlighted including fragilysin^[72]. This extracellular 20 kDa zinc-dependent metalloproteinase metabolite, produced by *B. fragilis*, could hydrolyze the extracellular domain of E-cadherin and activate the β -catenin nuclear signaling, leading to induction of CRC^[73]. Meanwhile fragilysin can damage the tight junction of the intestines, increases intestinal permeability^[74]. Colibactin is a bacterial-derived genotoxin first reported in 2006 by Nougayrede and colleagues. It is a hybrid polyketide-non ribosomal peptide produced through an intricate biosynthetic mechanism and encoded by the *pks* pathogenicity island^[75]. *E. coli* strains harboring this *pks* island were found to be associated with CRC^[76]. Moreover, colibactin, a kind of bacterial toxin synthesized by the *pks* genomic island can trigger chromosomal instability and DNA damage that might lead eventually to CRC^[77].

GUT MICROBIOTA AND EPIGENETIC MODIFICATION

Several epigenetic changes are common in CRC including DNA methylation, histone modification, and miRNA-mediated post-transcriptional regulation^[28,78]. Abnormal epigenetic modifications (AKA epimutations) occur in the promoter regions of tumor-suppressor genes and proto-oncogenes. These epimutations were reported in several

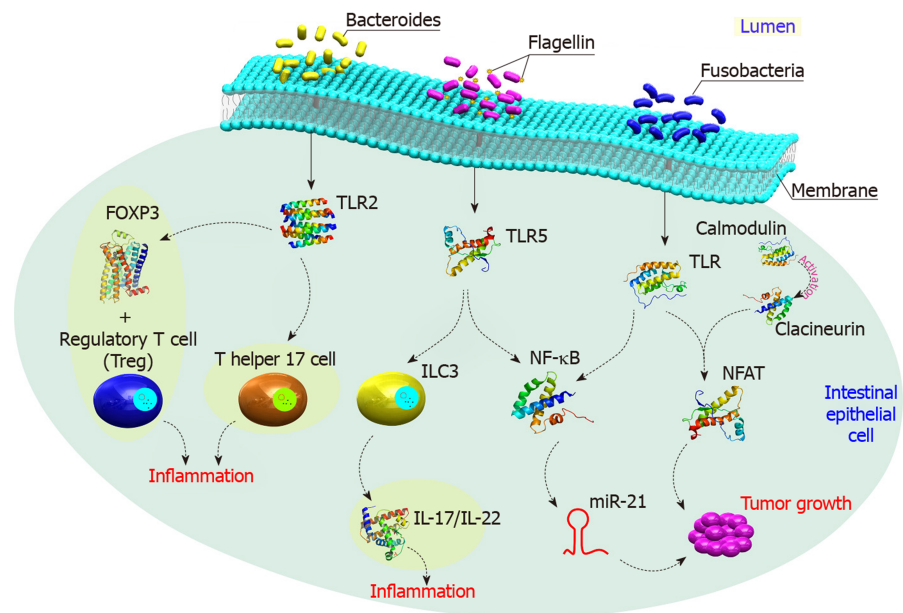


Figure 4 Different gut microbiota generate different oncometabolites. Bacteroides expresses specific signaling substances to activate toll-like receptor 2 (TLR 2), which functions in two different ways; activation of FOXP3 to trigger Treg activation leading to inflammation. The other way is the activation of T helper 17 cells that also triggers inflammation. Flagellin, a product of flagellated bacteria, activates also TLR 5 to activate innate lymphoid cells 3 and then IL 17 and 22 that initiate inflammation. TLR 5 also works on nuclear factor κ B to activate miR-21 that has a role in initiating cancer carcinogenesis (CRC). Meanwhile, *Fusobacteria* can stimulate a specific type of TLR that activates nuclear factor of activated T cell via calmodulin-based calcineurin to initiate CRC. CRC: Colorectal cancer; IL: Interleukin; ILC: lymphoid cells; NF- κ B: Nuclear factor- κ B; NFAT: Nuclear factor of activated T cell; TLR: Toll-like receptor; Treg: T regulatory cell.

malignancies including CRC, where many genes such as *MLH1*, *LKB1*, *APC*, *p16INK4a*, and *GATA4* represent common targets^[2,40,79]. Microbial community in our guts are armed with an arsenal of genes that produces millions of proteins, *let alone* their outpouring of metabolites^[67,80]. This microbiota produces low-molecular-weight substances that interact within the human cells with different targets to trigger genomic and epigenomic changes^[81]. Research teams everywhere highlight the association between gut microbiota and human diseases; thus, all these diseases should be revisited once again to elucidate the actual role played by microbial community. Being very stable, DNA might not be affected by microbial metabolites, and this is pointing to a more fragile component in our cells; epigenome.

DNA methylation

Linking diseases to epigenetic changes was first addressed in 1983^[82]. Based on that first note, numerous researches indicated that cancer cells undergo global hypomethylation along with site-specific hypermethylation in the promoters of cancer-related genes^[83]. A bunch of reports have indicated that the microbial metabolites can modulate epigenetic landscape of the host gut's cells *via* modifying the methylation pattern of cancer-related genes, as they represent a validated source of microbial-induced epigenetic change. Thus, the deep understanding of how epigenetic modifications influenced by the gut microbiota take place could offer possible therapeutic targets to prevent and treat CRC^[10,80].

In DNA methylation, DNMTs add methyl group (CH_3) to the fifth carbon atom in the cytosine residue using the intracellular methyl substrate *S*-Adenosyl methionine (SAM) as a methyl donor to convert the normal cytosine into 5-methylcytosine (5-mC)^[84]. Meanwhile, ten-eleven translocation enzyme can reverse this process *via* the oxygenation of 5-mC to produce 5-hydroxymethylcytosine^[85]. It is well known that folate is the main source of SAM, and this vitamin could be produced by *Bifidobacterium* and *Lactobacillus*, common probiotic bacteria^[86]. Folate is required for DNA methylation (5-methyltetrahydrofolate) or DNA synthesis (5-formyltetrahydrofolate and 5, 10-methenyltetrahydrofolate)^[87]. A study indicated that volunteers administered *Bifidobacterium* showed a high concentration of folate in their feces, meaning that these probiotic bacteria were capable to generate it and hence, affect DNA methylation pattern^[88]. On the other hand, deficiency of folate synthesis might contribute to DNA hypomethylation, which is an established phenomenon in CRC^[89]. Meanwhile, pathogenic bacteria such as *Helicobacter pylori* that infects the

stomach and causes gastritis or gastric ulcers or in severe infection gastric cancer can induce several epigenetic changes^[90]. A comparison between gastric biopsies excised from patients with gastritis (upon infection with *Helicobacter pylori*) and healthy individuals showed that chronic gastritis was associated with promoter hypermethylation of *E-cadherin* (*CDH1*), *MGMT*, *WIF1*, and *MLH1*^[91]. Although studies that address the relationship between the microbiome and epigenetic changes in CRC are rare, a population-based study reported that *Fusobacterium nucleatum* was associated with genomic hypermutation independent of *CIMP* and *BRAF* mutations^[92]. Other study indicated that *Fusobacterium* was correlated with the *CIMP* phenotype, wild-type *TP53*, *hMLH1* methylation, genomic hypermutation, and *CHD7/8* mutation^[93]. These studies strongly suggest the contribution of *F. nucleatum* to the epigenetic changes.

Histone modification

In addition to DNA methylation changes, histone modification patterns are also altered in human cancers^[84,94]. Some bacterial metabolites such as short chain fatty acids (butyrate and acetate) can induce epigenetic changes in colonic cells^[23,45]. Butyrate, a byproduct of the fermentation process of undigested dietary carbohydrates and proteins carried out by *Firmicutes*, has been shown to regulate over 4000 genes including many involved in apoptosis and cell cycle regulation^[95]. It is known also to inhibit histone deacetylases and induce hyperacetylation of histones, that lead to changes in the expression of critical cell cycle regulatory genes such as *CCND3* and *CDKN1A* in intestinal cells. Butyrate triggers epithelial generation of ROS and function also to suppress NF- κ B, the protein complex controls DNA transcription^[44,96]. Furthermore, *Bacteroides thetaiotaomicron* stimuli the inflammatory signaling by inhibiting NF- κ B pathway through binding to I κ B (inhibitor of κ B), inhibitory component of the NF- κ B pathway^[97]. It was reported that infection with *Listeria monocytogenes* (*L. monocytogenes*) can cause deacetylation of histone H3K18 in many genes in colonic cells such as *SMAD1*, *IRF2*, *SMARCA2* and *CXCL12*^[98]. *L. monocytogenes* execute the deacetylation process by translocating NAD-dependent deacetylase sirtuin 2 to the host nucleus. By doing so, *L. monocytogenes* epigenetically regulates cell cycle-related genes and modulate the host immune response to enable its invasion^[99].

MICRORNAS (MiRNAs) AND CRC

MiRNAs are a class of small single-stranded non-coding RNA molecules that are evolutionarily conserved and encoded by nearly 1% of the genome in most species^[100]. MiRNAs were found to be involved in initiation, progression, and metastasis of CRC, where it regulate of various cancer-related gene expression at the post-transcriptional level^[101]. Deregulated miRNAs identified in different types of cancers might put us a step forward towards understanding the tumor microenvironment, which necessitate deep investigation of their actual role in cancer progression and spreading^[102]. Numerous miRNAs were found to be associated with CRC, such as miR-21, Let-7, miR-145, miR-221, miR-17-19 cluster, and miR-143^[103]. Table 2 highlights some of miRNAs related to CRC development, progression, and metastasis. Studies addressed the expression levels of different miRNA in CRC, reported that miR-31, miR-20, miR-25, miR-223, miR-133b, miR-92, miR-93, miR-135a, miR-203, miR-183, and miR-17 were upregulated in CRC, while miR-26b, miR-192, miR-145, let-7a, miR-143, miR-215, miR-16, and miR-191 were downregulated in patients with CRC^[13,104]. Some miRNAs were suggested to serve as diagnostic markers for CRC, including miR-133a, miR-145, miR-484-5p, miR-139, miR-143, and miR-106a^[105], while another study indicated different set of miRNAs that could be used as biomarkers, including miR-125b, miR-125a, miR-143miR-30a-3p, and miR-145^[106]. However, this variation in miRNA list might be attributed to the samples used in the identification process (cell line, tissue, blood or stool) and to the techniques employed. Reports also highlight the role of human diet in modulating the expression of miRNA^[107]. For example, butyrate was found to regulate the expression of Let-7, miR-18-106a, miR-25-106b, and miR-17-92a in CRC^[96]. The later miRNA cluster (miR-17-92a) was found to be associated with c-Myc to inhibit the activity of PTEN and promotes PI3K-Akt-mTOR axis raising the cell survival in early stage adenoma in CRC^[108].

CONCLUSION

Gut microbiota is an enhancer to our second brain; the intestine. With millions of

Table 2 A list of representative miRNAs identified in tumor tissues that are of prognostic value in CRC patients

miRNA	Role in CRC	Ref.
miR-15a/ miR-16	Their low expression levels were associated with poor disease-free survival and overall survival	[124]
miR-17-5p	Its high expression was associated with disease-free survival	[125]
miR-21	Its high level of expression was associated with poor survival and poor therapeutic outcomes	[126]
miR-29a	Its elevated level of expression was associated with a longer disease-free survival in stage II CRC patients	[127]
miR-34a-5p	Its high expression was correlated with disease-free survival	[128]
miR-106a	Its downregulation was associated with shortened overall survival	[125]
miR-132	Its decreased expression level was associated with poorer overall survival and occurrence of distant metastasis especially in liver	[129]
miR-150	Its elevated expression level was associated with longer overall survival. While its low level of expression was associated with poor therapeutic outcome in patients treated with 5-Fluoro uracil	[130]
miR-195	Its low expression rate was associated with occurrence of lymph node metastasis and advanced tumor grade/stage	[131]
miR-199b	Increased in metastatic CRC tissue compared with non-metastatic CRC tissue. Furthermore, its low expression was associated with longer overall survival	[132]
miR-203	Its elevated expression level was associated with advanced TNM staging and poorer overall survival	[130]
miR-320e	Its high expression was associated with poorer overall survival in stage III colon cancer patients	[133]
miR-429	Its overexpression was associated with overall survival; low level of expression was associated with response to 5-Fluoro uracil-based chemotherapy	[134]
miR-494	Its elevated expression was associated with shorter DFS and overall survival	[135]
miR-625-3p	High expressions were associated with higher overall survival and enhanced response to therapy	[136]

CRC: Colorectal cancer.

proteins expressed by the microbiota's arsenal, human could make use of various kinds of dietary ingredients, that otherwise will be rubbish-in/rubbish-out. Although genetic factors and age play a role in the pathogenesis of CRC, still gut microbiota has the lion's share in this complicated process. Armed with an enormous number of identified and yet-to-be-identified metabolites, this population of bacteria can modify the gut's cells methylation pattern and histone structure causing inflammation, that lead eventually to cancer. It is quite important to keep these microorganisms under focus by deeply investigate their intricate communications with our cells. By doing so, we would be able to avoid at least life-threatening diseases such as CRC^[1].

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