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## **Microbiota regulation in constipation and colorectal cancer**

Wang LW *et al.* Regulation of microbiota

Li-Wei Wang, Hao Ruan, Bang-Mao Wang, Yuan Qin, Wei-Long Zhong

### **Abstract**

The relevance of constipation to the development and progression of colorectal cancer (CRC) is currently a controversial issue. Studies have shown that changes in the composition of the gut microbiota, a condition known as ecological imbalance, are correlated with an increasing number of common human diseases, including CRC and constipation. CRC is the second leading cause of cancer-related deaths worldwide, and constipation has been receiving widespread attention as a risk factor for CRC. Early colonoscopy screening of constipated patients, with regular follow-ups and timely intervention, can help detect early intestinal lesions and reduce the risks of developing colorectal polyps and CRC. As an important regulator of the intestinal microenvironment, the gut microbiota plays a critical role in the onset and progression of CRC. An increasing amount of evidence supports the thought that gut microbial composition and function are key determinants of CRC development and progression, with alterations inducing changes in the expression of host genes, metabolic regulation, and local and systemic immunological responses. Furthermore, constipation greatly affects the composition of the gut microbiota, which in turn influences the susceptibility to intestinal diseases such as CRC. However, the crosstalk between the gut microbiota, constipation, and CRC is still unclear.

**Key Words:** Microbiota; Constipation; Colorectal cancer; Intestinal microenvironment; Immunological responses; Metabolic regulation

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**Core Tip:** <sup>5</sup> The changes in the composition of the gut microbiota are correlated with an increasing number of common human diseases, including colorectal cancer (CRC) and constipation. <sup>7</sup> CRC is the second leading cause of cancer-related deaths worldwide, and <sup>11</sup> constipation has been receiving widespread attention as a risk factor for CRC. An increasing amount of evidence supports the thought that gut microbial composition and function are key determinants of CRC development and progression, with alterations inducing changes in the expression of host genes, metabolic regulation, and local and systemic immunological responses.

## INTRODUCTION

There are approximately 100 trillion microbial cells in the gut microbiota, including a varied mix of bacteria, fungi, protozoa, and viruses<sup>[1]</sup>. Most gut bacteria form complex networks that are important mediators of tissue homeostasis, inflammation, and tumor development<sup>[2]</sup>. Despite regularly being described to as the “forgotten organ,” the symbiotic equilibrium of the gut microbiota plays a crucial role in maintaining host health<sup>[3]</sup>. The gut microbiota is involved in a variety of physiological activities in the host, such as the fermentation of food components, production of short-chain fatty acids (SCFAs), regulation of immune function, regulation of the growth and differentiation of intestinal epithelial cells (IEC), bile salt metabolism, and production of vitamins and other protective substances. It also acts as a biological barrier to prevent the adhesion and invasion of pathogenic and potentially pathogenic bacteria. This intricate ecosystem not only involves a passive colonizer of the gut, but it also facilitates engagement with the host through a variety of interactions that support a number of physiological functions, including nutrition absorption, immunity, metabolism, and tissue development<sup>[4,5]</sup>.

Colorectal cancer (CRC) is the third most prevalent type of cancer, accounting for nearly 2 million new cases each year, and is the second leading cause of cancer-related deaths globally<sup>[6]</sup>. As with many other diseases, the onset and progression of CRC are due to a combination of hereditary and environmental factors. The microbiota is an essential environmental component that contributes to the development of cancers such as colorectal, liver, biliary tract, and breast cancers<sup>[7]</sup>. The microbiota in the colorectum interacts with IEC to obtain energy and regulate the body's immune response; consequently, its role in colorectal carcinogenesis is of great interest.

Constipation is a common gastrointestinal disorder and a common symptom in patients with cancer. It is characterized by scanty stools, hardened stools, or difficulty passing stools, and may occur alone or secondary to other diseases<sup>[8]</sup>. Constipation is a common problem for 16% of individuals overall and 33.5% of seniors (60-101 years)<sup>[9]</sup>. Disruption of the intestinal microbial community (ecological dysbiosis) can lead to

various changes in host pathophysiology, resulting in functional gastrointestinal disorders, particularly constipation<sup>[10]</sup>.

### **MICROBIOTA-INDUCED REGULATION OF CRC**

It is widely accepted that a variety of variables, including heredity, the environment, and chronic inflammation, contribute to the etiology of CRC<sup>[11]</sup>. Moreover, inflammation is a recognized driver of CRC development<sup>[2,12]</sup>. The gut microbiota can affect inflammatory processes in the digestive system as part of its interaction with the host immune system. When feces from patients with CRC were instilled into sterile, carcinogen-fed mice, the gut microbiome promoted the synthesis of chemokines, which increased histological inflammation and the expression of inflammatory genetic markers<sup>[13]</sup>. This is because the gut microbiota stimulates the production of chemokines (*e.g.*, CCL5, CXCL9, CXCL10, CCL17, and CCL20) through tumorigenic cancer cells, thus favoring the recruitment of beneficial T cells into tumor tissue<sup>[14]</sup>. The microbiome induces multiple cases of inflammation and activates oncogenic pathways, resulting in increased cytokine expression during inflammation.

The intestinal mucosal barrier usually keeps the immune cells and gut microbiota apart. IECs make up the single layer of the intestinal mucosal barrier, which is joined by tight junctions<sup>[15]</sup>. The intestinal mucosal barrier is extremely permeable in both humans and CRC mouse models<sup>[16]</sup>. Increased susceptibility to CRC due to dextran sodium sulfate-induced colitis disrupts the function of the intestinal mucosal barrier<sup>[17]</sup>. The mucosal barrier in rats is compromised by ammonia, a product of the intestinal microbiota, which has also been associated with an increase in colonic adenomas<sup>[18]</sup>. Sulfides are toxic to colon cells and inhibit butyrate oxidation, which can damage the barrier of the colon cell<sup>[19]</sup>. Notably, even some metabolites can enhance the mucosal barrier function of the intestine. SCFAs are essential nutrients for IEC, which encourage the proliferation and differentiation of these cells and maintain the integrity of the intestinal epithelium<sup>[20]</sup>.

Pattern recognition receptors (PRRs) enable communication between the immune system and microbiota by recognizing specific molecular patterns associated with pathogens<sup>[21]</sup>. In animal models, these PRRs are present among those associated with coliform-associated carcinogenesis, including Toll-like receptors (TLRs)<sup>[22]</sup>, nucleotide-binding oligomerization-like receptors, retinol-induced gene-I-like receptors<sup>[23]</sup>, and melanoma 2-like receptors<sup>[24]</sup>. When myeloid differentiation factor 88 (MyD88), a crucial bridge protein required for TLR signaling, is activated, invasive commensal bacteria and their components bind to the TLRs on tumor-infiltrating myeloid cells<sup>[25]</sup>. This in turn triggers the synthesis of downstream pro-inflammatory cytokines, including IL-23, IL-17A, IL-6, IL22, IL-1 $\beta$ , and TNF- $\alpha$ <sup>[14,16,25]</sup>. These cytokines promote malignant progression by enhancing cell proliferation, aggressiveness, and resistance to apoptosis. Ultimately, they stimulate the signaling pathways for nuclear factor-B (NF-B) and activator of transcription 3 (STAT3), which enhances tumor cell growth<sup>[26,27]</sup>. Additionally, commensal bacteria and their metabolites boost the expression of IL-17C in transformed IECs via TLR/MyD88-dependent signaling. IL-17C promotes tumor cell survival and carcinogenesis by inducing the expressions of B-cell lymphoma-2 and B-cell lymphoma-xL in IECs in an autocrine manner<sup>[25]</sup>.

According to previous studies, oncogenesis can be undertaken using a number of bacteria, such as *Fusobacterium nucleatum* (*F. nucleatum*) adhesion and the invasion of colonic epithelial cells, to regulate oncogenic and inflammatory responses through FadA antigen binding to E-calmodulin on IECs to activate  $\beta$ -linked proteins<sup>[28]</sup>. Through the activation of TLR-4 signaling to NF- $\kappa$ B and the upregulation of miR-21 expression, myeloid cell infiltration is induced in tumors, and cancer cell proliferation and tumor progression are promoted<sup>[29]</sup>.

In addition to the inflammatory immune mechanisms of gut microbes, the gut microbiota is capable of producing proteins, molecules, and secondary metabolites that are especially harmful to DNA. Host DNA can directly interact with and be modified by these products<sup>[30]</sup>. Bacteria produce two well-defined genotoxins: Cytolethal distending toxin (CDT) and colistin<sup>[31]</sup>. Several enteric pathogens, including *Salmonella*, *Escherichia*



and *Campylobacter* spp. produce CDT, which induces double-stranded DNA breaks through its deoxyribonuclease activity<sup>[32,33]</sup>. In the form of a deoxyribonuclease I-like protein, CDT exhibits DNA enzyme activity and regulates cell cycle development<sup>[34]</sup>. This toxin causes eukaryotic cells to stagnate in the G2 /M transition phase of the cell cycle, which stops the division of eukaryotic cells, but the cytoplasm continues to grow and expand. At last, the nucleus was seriously damaged and chromatin was obviously broken or completely disappeared<sup>[35]</sup>. *Bacteroides fragilis* (*B. fragilis*) toxins can lead to CRC progression by inducing mutations, damaging DNA, and ultimately damaging the epithelial cell genome<sup>[36]</sup>. Upon IECs exposure, *B. fragilis* toxin binds to specific IEC receptors and rapidly cleaves the extracellular structural domain of E-cadherin, leading to complete degradation of E-cadherin<sup>[37]</sup>. Subsequently,  $\beta$ -linked protein/T-cell factor-dependent transcriptional activation induces transcription and translation of the c-Myc oncogene and sustained cell proliferation<sup>[38]</sup>. Furthermore, both *B. fragilis* toxins and *Enterococcus faecalis* reactive oxygen species have been linked to strand breaks and chromosomal aberrations *in vitro*<sup>[39,40]</sup>. Because small-molecule inhibitors that target the production of *Escherichia coli* (*E. coli*) toxins have been demonstrated to reduce the tumor burden in mouse models, their binding or inactivation may have therapeutic or preventative effects on CRC<sup>[40]</sup>.

Besides, *Clostridium perfringens* belongs to the genus *Clostridium*, which produces bile acid hydrolases that catalyze the production of secondary bile acids (such as deoxycholic acid and lithocholic acid). Increased secondary bile acids levels activate the Wnt/ $\beta$ -linked protein and NF- $\beta$  signaling pathways, resulting in oxidative DNA damage, increased mitotic activity, and activation of intrinsic apoptotic pathways such as mitochondrial cytochrome C release and oxidative stress<sup>[41,42]</sup>. Secondary bile acids also influence CRC by activating the bile acid receptors G protein-coupled bile acid receptor 5 (TGR5) and farnesoid X receptor (FXR)<sup>[43,44]</sup> (Figure 1).

## MICROBIOTA-INDUCED REGULATION OF CONSTIPATION

It is widely accepted that gut dysfunction, such as intestinal fluid transport, intestinal peristalsis, mucus production, and intestinal nerve conduction disorders, is the primary cause of constipation<sup>[45]</sup>. However, several recent studies have demonstrated that the gut microbiota and its metabolism play a significant role in the physiology and pathology of constipation. They have the capacity to change intestinal secretion and the microenvironment by interacting with the immune system, enteric nervous system (ENS), and central nervous system<sup>[46]</sup>. Therefore, gut microbiota may cause intestinal motility disorders through complex mechanisms, but the key underlying mechanisms are still under investigation.

In a constipated state, intestinal motility and secretion can become abnormal if the gut microbiota and metabolism are disrupted<sup>[47]</sup>. Simultaneously, the host modulates the gut microbiota via a variety of PRRs. In terms of the regulation of gastrointestinal motility, most TLRs are expressed in gut microbial components and gastrointestinal sensory components<sup>[48,49]</sup>. TLRs can communicate directly with bacterial components to make it easier for gastrointestinal cells and the gut microbiota to work together. For example, there is evidence of the expression of TLR2 in intestinal smooth muscle cells, neurons, glial cells, and interstitial cells of Cajal (ICCs). By binding to TLR2 from the gut microbiota, lipopeptides, peptidoglycan, and lipophilin acid trigger the release of glial cell line-derived neurotrophic factor via NF- $\kappa$ B and p38 mitogen-activated protein kinase (MAPK) signaling, maintain ENS and neurogenesis neurons, and exert anti-inflammatory effects to improve gastrointestinal motility in a manner that is not dependent on MyD88<sup>[48,50]</sup>.

Of the receptors previously described, TLR4 is the most suitable for recognizing lipopolysaccharides (LPS) generated from the gut microbiota, along with TLR2. When LPS binds to TLR4 expressed on myeloid macrophages (MM), it induces the production of bone morphogenetic protein 2 (BMP2), which improves gastrointestinal motility. Enteric neurons generate colony-stimulating factor 1 in conjunction with BMP2, which facilitates MM homeostasis and regulates gastrointestinal motility<sup>[51]</sup>. As a result, the gut microbiota participates in and regulates the crosstalk between the MM and gut neurons,



thereby influencing gastrointestinal dynamics. Nevertheless, higher concentrations of LPS expressed on ICCs, cause them to bind to TLR4 and inhibit pacemaker activity in ICC<sup>3</sup> via the MAPK and NF- $\kappa$ B signaling pathways, thereby suppressing gastrointestinal motility and leading to reduced fecal production and prolonged defecation<sup>[52]</sup>.

Furthermore, gut microbes can interact with ENS not only through TLRS but also through the intestinal serotonin network to promote the functional maturation of the enteric neural network. This promoted the synthesis and release of serotonin (5-HT) through the action of SCFAs on enterochromaffin cells<sup>[53]</sup>. 5-HT is a key regulator of gastrointestinal motility and secretion, and consists mainly of 5-HT<sub>1</sub>, 2, 3, 4, and 7 isoforms, all of which have the ability to act directly on the various receptors on epithelial cells, smooth muscle cells, and enteric neurons, thereby affecting smooth muscle relaxation and contraction<sup>[54,55]</sup>. Notably, 5-HT is also a major product of tryptophan metabolism. The dysregulation of tryptophan metabolites significantly contributes to the etiology of colonic dysmotility<sup>[56,57]</sup>. The creation of indole-3-methanol by the microbiota stimulates<sup>1</sup> aryl hydrocarbon receptors in myenteric neurons, allowing them to respond to the microbial environment in the lumen<sup>1</sup>. It also triggers neuron-specific effector mechanisms and the expression of colonic motility<sup>[58]</sup>.

Similarly, the intestinal flora produces gas, which has a significant impact on intestinal motility. Methane, hydrogen, hydrogen sulfide, and carbon dioxide are among the gases generated by gut microorganisms in the digestive tract. In the gastrointestinal system, unabsorbed carbohydrates are fermented by bacteria, producing these byproducts. In fact, the lactulose hydrogen breath test reveals a substantial link between constipation-predominant irritable bowel syndrome and excessive methane levels<sup>[59]</sup>. The most prevalent methanogenic bacterium in the human gut is *Methanobacterium smegmatis* (*M. smegmatis*)<sup>[60]</sup>. A clinical study showed that *M. smegmatis* was overgrown in the intestines of constipated patients with elevated methane levels<sup>[61]</sup>. In addition, nitrate or nitrite from the gut lumen can serve as raw material for the production of NO by gut microbes<sup>[62]</sup>. It has been established that NO is an inhibitory neurotransmitter that may

contribute to reduced gastrointestinal smooth muscle tension and diminished gastrointestinal motility.

Bile acids function as physiological laxatives to modify water and electrolyte transport in the intestinal lumen, as well as to regulate intestinal motility. Bile acids stimulate the TGR5 in enterochromaffin cells and myelinated neurons, releasing 5-HT and calcitonin gene-related peptides<sup>[63]</sup>. Several studies have shown that ileal bile acid-transport protein inhibitors significantly reduce bowel passage time, and improve constipation symptoms when compared with placebos<sup>[64,65]</sup>. Gastrointestinal flora modulates **the gut microbiota**, regulates **the synthesis of hepatic bile acids**, and promotes the participation of pro-bile acids in various chemical reactions in the body, thereby increasing the diversity of bile acid derivatives<sup>[66]</sup>.

Consequently, the development of **functional maturation of the ENS**, and the reduction of **colonic** motility issues, may be aided by **microecological management that directly targets specific TLR and 5-HT signaling pathways**. At the same time, these findings support the hypothesis that the metabolism of Trp under the control of the gut microbiome is involved in host-microbiota crosstalk and gastrointestinal motility fine-tuning. This suggests that Trp metabolism may be a viable therapeutic target for gastrointestinal motility.

### **POSSIBLE MECHANISMS WHEREBY CONSTIPATION IS INVOLVED IN THE DEVELOPMENT OF CRC**

Because the etiologies of constipation and CRC are similar, it is unknown whether constipation and the emergence of CRC are causally related. Several hypothetical mechanisms may be behind the associations observed in this study. It has been theorized that lower bowel motility, and correspondingly longer transport time, in constipated patients would increase the risk of CRC due to prolonged exposure of the colonic mucosa to fecal carcinogens. Second, it has been suggested that constipation may accelerate the onset of CRC by causing immunological abnormalities and gene mutations or deletions *via* the disruption of intestinal microecology. Furthermore, harmful compounds released

by microbial cells are thought to spread to other regions of the body, leading to the development, initiation, or progression of cancer<sup>[67,68]</sup>. Additionally, any relationship with constipation may be due to inverse causality; in other words, CRC may cause constipation before the clinical manifestation of cancer. Eventually, although CRC is more likely to be detected later than constipation is usually detected, the two conditions may be separate but converging disorders caused by similar underlying risk factors. Therefore, although constipation is not an indication for a colonoscopy, it should be considered in specific individuals (e.g., those over 50 years of age) for colon cancer screening<sup>[8]</sup>.

While associations have been drawn between constipation and CRC in prior studies, the results are contradictory<sup>[69,70]</sup>. Generally, these studies were often constrained by selection bias, recollection bias, and self-reported data on constipation. The specific relationship between constipation and CRC is not fully understood, and in this context, the gut microbiota may be the key to solving this mystery.

The type and amount of gut microbiota and their metabolites differ between patients with constipation and the healthy population. The abundances of *lactococci*, *rumenococci*, *E. coli*, and *Staphylococcus aureus* in the intestinal flora were considerably higher in the stool of patients with constipation, whereas the abundances of *bifidobacteria* and *lactobacilli* were significantly lower, resulting in severe dysbiosis<sup>[71,72]</sup>. The abundance of *Bacillus* spp. in the colonic mucosa is significantly higher not only in patients with constipation, but also in those with CRC<sup>[73,74]</sup>. In addition, when constipation occurs, because dry, hard stools remain in the colon for an extended period of time, they easily consume the mucus of the loose external mucus layer of the intestine. This creates an opportunity for imbalances in the gut microbiota to invade the internal mucus layer, thereby inducing an immune response and causing inflammation, which is a necessary trigger for CRC<sup>[47]</sup>.

The presence of *B. fragilis*, *E. coli*, and *F. nucleatum* in the intestine may also induce the abnormal expression of pro-oncogenes and oncogenes, as well as abnormal mismatch chromosome repair. By doing so, it may trigger cellular heterogeneous hyperplasia and adenomatous polyps, and contribute to the emergence and spread of CRC<sup>[75-77]</sup>. The

increased abundance of *F. nucleatum* and *E. coli* may be involved in colorectal carcinogenesis and development by activating the Wnt and NF- $\kappa$ B signaling pathways, which promote the release of chemokines, adhesion molecules, and pro-inflammatory cytokines. These pathways can even induce chromosomal instability and the abnormal methylation of CpG islands to mediate immune cell aggregation, thereby inducing apoptosis and regulating the tumor immune microenvironment. Notably, altered abundance of *E. fragilis* can induce signal transducer and STAT3 activation in colonic epithelial cells, and *Enterococcus faecalis* can induce the formation of reactive oxygen species, related oxidative stress, and DNA damage. This in turn may cause cell proliferation, apoptosis, and abnormal immune responses, leading to colorectal tumor development<sup>[78]</sup>.

Simultaneously, aberrant metabolites of the gut microbiota caused by intestinal microecological dysregulation are also involved in the development and progression of colorectal diseases. In addition to anti-inflammatory and immunomodulatory effects, moderate amounts of butyrate can enhance the defense of the gastrointestinal mucosal barrier. They can also lessen colon cancer cell propagation and migration by increasing the production of mucin-encoding genes; activating the activity of heat shock proteins, trefoil factors, antimicrobial peptides, and glutaminyl transferases; and inhibiting histone deacetylases<sup>[79]</sup>. However, excessive amounts of butyrate not only inhibit the release of mucin by intestinal cup cells and encourage the absorption of water and electrolytes from the colon, but they also inhibit the contraction of colonic smooth muscle and reduce the movement of the colon. This leads to constipation and may even promote the proliferation of tumor cells or increase the activity of  $\beta$ -catenin, thereby increasing the risk of tumor development<sup>[80]</sup>.

## **CONCLUSION**

Constipation may be involved in the process of CRC development and progression *via* a mechanism that may involve changes in the composition of the flora, and abnormalities in its metabolites caused by dysbiosis of the intestinal flora, leading to intestinal motility

dysfunction and/or abnormalities in the immune microenvironment, as shown in Figure 2. The pro-tumorigenic effects of individual cytokines are context-dependent and significantly affected by synergistic effects in a complex cytokine environment.

The crosstalk between the gut microbiota, constipation, and CRC, and their specific mechanisms of action, are still poorly understood. Nevertheless, they also provide a wealth of new ideas and prospective targets for the prevention and treatment of CRC. The direction of relevant gut microbial research is still dominated by animal studies, and there remain numerous obstacles to be overcome in clinical treatment owing to individual variations, tumor staging, and cross-species translation. To further understand the relationship between the gut microbiota, constipation, and CRC, ongoing preclinical and clinical research is required.

The future study design is as follows: Subjects first need to be pretreated with fecal sample sequencing and macrogenome sequencing, and oral antibiotics to deplete the natural gut microbes. Patients then undergo fecal transplantation and periodic fecal testing with sigmoid biopsy and tumor biopsy at appropriate times to observe the effects of fecal transplantation on constipation and CRC and assess the safety, feasibility, and impact of fecal transplantation on the intestinal microenvironment in patients with constipation and CRC. Future studies should clarify which patients can receive fecal transplants and which donor gut microbes are effective. In addition, the timing of antibiotic pre-treatment all need to be further investigated. Gut microbiota may soon become a potent tool in the battle against CRC.

According to the latest guidelines on constipation, although constipation itself is not an indication of colonoscopy, patients with severe chronic constipation or alarm symptoms should consider colonoscopy to screen for CRC. In addition, CRC screening is not a "one size fits all" concept due to the variable incidence of recognized CRC risk factors. It is now recognized that those people identified as having a greater risk for CRC, such as those with a family history of CRC or CRC-associated genetic illnesses, should be examined at a younger age and using colonoscopy. The guidelines recommend that colonoscopy be started before age 50 or even at age 45 for patients with associated risk



factors, or after age 50 if there are no associated risk factors and timely interventions should be made to reduce the risk of developing colorectal polyps and CRC to prevent disease progression.

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