Bidirectional regulation of bile acid on colorectal cancer through bile acid-gut microbiota interaction

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Abstract: Colorectal cancer (CRC) is now the third most common malignancy and the second leading cause of cancer death globally. Bile acid has bidirectional regulatory effects on CRC and influences its progression by interacting with gut microbiota. In this review, we provide evidence for bidirectional regulation of bile acid on CRC at multi-level and discuss the communication of gene, immune, metabolism, and diet in the context of CRC with bile acid-gut microbiota interaction. The study on bidirectional regulation of bile acid is helpful to provide a more comprehensive and in-depth understanding of CRC pathogenesis and expect to be a new option for the treatment of CRC.

Keywords: Bile acid, gut microbiota, colorectal cancer, short-chain fatty acids, diet, methylation

Introduction

According to an estimate from International Agency for Research on Cancer (IARC) in 2018, there are about 1.8 million new cases and 900,000 deaths of colorectal cancer (CRC) annually, making it the third most common malignancy and the second leading cause of cancer death globally. And the incidence of CRC tends to increase in younger population [1-4]. Bile acid is synthesized from cholesterol in hepatocytes through a series of reactions under the action of hepatocellular enzymes and gut microbiota. In accordance with different structure and source, bile acid can be divided into primary and secondary bile acid, free bile acid and conjugated bile acid [5-7].

Normal microorganisms live and keep in a dynamic balance with human body. The first link between gut microbiota and CRC is found in 1975 [8]. Metagenomic and metataxonomic studies show that a higher relative abundance of putatively pro-carcinogenic microbial species such as Fusobacterium nucleatum, Escherichia coli (E. coli), B. fragilis, Enterococcus faecalis (E. faecalis), Streptococcus gallolyticus and Peptostreptococcus spp. and a lower level of protective genera such as Roseburia, Clostridium, Faecalibacterium and Bifidobacterium, present in CRC patients. When gut microbiota of CRC patients transfers to germ-free mice by fecal microbiota transfer (FMT), Fusobacteria, Parvimonas, Butyrivibrio, Gemella and Akkermansia muciniphila (A. muciniphila) show a higher proportion, while Ruminococcus, Bifidobacterium, Eubacteria and Lachnospira show a lower proportion. Among them, Parvimonas and Parasutterella are more abundant in CRC patients and are related to a high fat intake, which will probably result in more enteric deoxycholic acid (DCA) release and co-exclude anti-inflammatory bacteria such as Faecalibacterium, Eubacterium and butyrate producing bacteria Firmicutes species.

Interaction between bile acid and gut microbiota is involved in many metabolic processes and immune responses of body, playing a bidirectional role in regulating CRC. On the one hand, bile acid regulates intestinal inflammation and tumorigenesis in a variety of ways, which is accompanied by changes in gut microbiota, thus inhibiting inflammation associated tumorigenesis and dampening progression of tumor. On the other hand, bile acid causes a series of changes in host, including intestinal barrier destruction, immune responses imbalance,
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Abnormal signaling pathways and DNA methylation by interacting with gut microbiota.

In brief, bile acid has bidirectional regulation on CRC and the underlying mechanism may be closely related to gut microbiota. Gene, immune, metabolism and diet are also involved in the interplay and affect tumor progression. Study of bile acid bidirectional regulatory effect is helpful to provide a more comprehensive and in-depth understanding of CRC pathogenesis and expect to be a new option for the treatment of CRC.

Bile acid as therapeutic targets for CRC

At cellular level, ursodeoxycholic acid (UDCA) inhibits the formation and growth of human colonic tumor cell lines such as HT29 and HCT116 by activating phosphorylation of p38 and Erk1/2, inducing cycle arrest from G2/M phase to S phase and diminishing oxidative damage induced by reactive oxygen species (ROS) [9]. Moreover, UDCA inhibits tumor cell resistance to apoptosis and increases their sensitivity to chemotherapeutic agents CPT-11 by preventing nuclear factor kappa B (NF-kB) and downregulating COX-2 of HCT116 cells [10]. Besides, UDCA enhances the cytotoxicity of HT-29 cells, which is induced by anti-tumor drug vorinostat through inhibiting expression of Nrf-2 gene and regulating the redox status of tumor cells, thereby reducing proliferation and total number of CRC cells and delaying tumor progression [11, 12].

Colitis-associated carcinogenesis (CAC) animal model induced by dextran sulfate sodium (DSS) is similar to human CAC in etiology, tumor type, distribution and gene expression. UDCA significantly suppresses the emergence and development of dysplasia, adenocarcinoma and squamous carcinoma in DSS induced CAC model [13]. For carcinogenic animal model induced by cholic acid (CA) and azoxymethane (AOM), UDCA suppresses tumor occurrence and progression to a certain extent [14, 15]. Primary sclerosing cholangitis (PSC)-inflammatory bowel disease (IBD) patients, especially those diagnosed with IBD under the age of 40 have higher risks for CRC and death compared to patients with IBD alone [16]. The first study about the protective effect of UDCA on ulcerative colitis (UC)-PSC patients is published in 2001, reported that UDCA reduces the incidence of colonic dysplasia in UC-PSC patients after adjustment for sex, duration and severity of disease and sulfasalazine use in a cross sectional study [17]. Moreover, UDCA prevents the progression of low-grade dysplasia (LGD) and reduces the need for immediate surgery in LGD and/or DNA-aneuploidy IBD patients [18]. Besides, a 20-year study of IBD-PSC patients shows that UDCA gradually decreases the annual incidence of CRC after 6 years. And 9 years later, no CRC is found in IBD-PSC patients [19] (Table 1).

As mentioned above, bile acid is capable of inhibiting tumor cell growth and formation, enhancing cell sensitivity to anti-tumor drugs and suppressing the inflammation-associated tumor, thereby contributing to delaying the progression of tumors at cellular, tissue and host level. Further study about the above effects is needed to elucidate the specific mechanisms of bile acid and its effects on CRC, and help for better understanding bile acid bidirectional regulation and making it as a promising treatment for CRC in the future.

Table 1. The regulatory effect of UDCA on CRC

<table>
<thead>
<tr>
<th>Subject (s)</th>
<th>Effect (s)</th>
<th>Ref (s)</th>
</tr>
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<tbody>
<tr>
<td>HT29 cells</td>
<td>Growth Proliferation↓, Oxidative Damage↓,</td>
<td>[3-6]</td>
</tr>
<tr>
<td></td>
<td>Antitumor Drug Sensitivity↑</td>
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<tr>
<td>HCT116 cells</td>
<td>Growth Proliferation↓, Oxidative Damage↓,</td>
<td>[3, 4]</td>
</tr>
<tr>
<td></td>
<td>Resistance to Apoptosis↓, Antitumor Drug</td>
<td></td>
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<tr>
<td></td>
<td>Sensitivity↑</td>
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<tr>
<td>DSS-induced CAC model</td>
<td>Prevalence of dysplasia, squamous carcinoma,</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>adenocarcinoma↓</td>
<td></td>
</tr>
<tr>
<td>CA, AOM induced CAC model</td>
<td>Tumor occurrence and progression↓</td>
<td>[8, 9]</td>
</tr>
<tr>
<td>UC-PSC patients</td>
<td>Colonic dysplasia incidence↓</td>
<td>[11]</td>
</tr>
<tr>
<td>IBD-PSC patients</td>
<td>CRC annual incidence↓</td>
<td>[13]</td>
</tr>
<tr>
<td>IBD patients</td>
<td>Low-grade dysplasia progression↓, Need for</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td>immediate surgery ratio↓</td>
<td></td>
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</tbody>
</table>

CRC: colorectal cancer; UDCA: ursodeoxycholic acid; DSS: dextran sulfate sodium; CAC: colitis-associated carcinogenesis; CA: cholic acid; AOM: azoxymethane; UC: ulcerative colitis; PSC: primary sclerosing cholangitis; IBD: inflammatory bowel disease.
Carcinogenic effects of bile acid on CRC

Although bile acid such as UDCA has some beneficial effects on CRC at multi-level, other bile acid may have carcinogenic effects on CRC to certain extent. In wounded colonic epithelial monolayers model, DCA prevents wound healing by impairing cell migration ability, which may be related to bile acid farnesoid X receptor (FXR) and cystic fibrosis transmembrane regulator (CFTR) [20]. In terms of intestinal barrier, DCA destroys cell monolayer integrity and upregulates proinflammatory cytokines production. MUC2, defensin and cryptdin secreted by goblet cells and Paneth cells are decreased after DCA administration. Normal intestinal barrier allows for absorption of nutrients and prevents pathogen invasion. Increased intestinal permeability leads to exposure of intestinal antigens to intestinal mucosa, activation of the immune system and increased inflammatory cell infiltration, which will result in the occurrence of chronic inflammation. Besides, DCA increases the level of opportunistic pathogens such as Ruminococcus, Escherichia-Shigella, Desulfovibrio, Dorea and reduces beneficial bacteria such as Lactobacillus, Lactococcus, and Roseburia [21]. Destruction of intestinal barrier deteriorates the imbalance of microbiota and further aggravates the occurrence of intestinal tumors [22].

In HCT116, DCA increases NF-κB and activator protein 1 (AP-1) DNA binding by reducing the level of IκB-α, inducing the generation and nuclear translocation of RelA. Increased and sustained expression of NF-κB and AP-1 is associated with tumor cell proliferation, transformation and resistance to apoptosis, which may promote transition from adenoma to carcinoma and play a role in colon carcinogenesis [9]. This is further confirmed in animal experiment that DCA decreases the apoptosis of intestinal tumor cells and increases the number of intestinal tumors with high grade dysplasia (HGD) or intramucosal carcinoma [22]. Besides, in intestinal carcinogenesis Apcmin/+ model, CA affects gut microbiota composition directly or indirectly and plays a role in the progression of intestinal adenoma. On the one hand, CA changes dominant intestinal phyla to Bacteroidetes, Verrucomicrobia increment and Firmicutes decrease. On the other hand, CA promotes DCA generation, which will further inhibit intestinal bacteria growth such as Clostridium perfringens. Although some reports reveal the benefit of A. muciniphila in intestinal inflammation, however, the characteristics of mucin degradation may limit its application. In Apcmin/+ model, CA increases the relative abundance of A. muciniphila and inhibits mucin-producing cells functions such as goblet cells and Paneth cells, thus impairing gut barrier function, facilitating intestinal pathogens colonization, and causing inflammation and carcinogenesis. Moreover, CA significantly decreases the fecal concentration of short-chain fatty acid (SCFA), which will inhibit its anti-inflammatory ability and may increase the risk of CRC partly [23].

Tauro-β-muricholic acid (T-βMCA) is a major driver of CRC development. Total bile acid and T-βMCA are associated with tumor load in Apcmin/+ mice from intestinal inflammation to initial tumor development and maximum tumor load. When T-βMCA is added to Apcmin/+ mice, intestinal integrity is destroyed, while intestinal permeability, tumor indexes, cytokines, tumor proliferation and growth are increased. The driving effect of T-βMCA on CRC is confirmed in CRC cell lines (HCT116 and HT29) and cancer stem cells (CSCs) experiments, in which T-βMCA drives CSC proliferation and increases the expression of intestinal stem cell markers. Further researches found that the effect of T-βMCA on CRC may be related to inhibition of FXR activity, which was demonstrated in CRC cell experiment. In addition, FXR agonists improves clinical symptoms, histopathological changes, intestinal barrier, systemic inflammatory response, bile acid homeostasis and tumor number in CRC animal models, indicating that T-βMCA promotes the development of CRC by dysregulating FXR signaling pathway. The early detection and timely treatment of abnormal bile acid expression and FXR signaling pathway are expected to be a potential therapeutic strategy for the prevention and treatment of CRC [24].

Normal microbial communities maintain harmony with dietary components and keep a symbiotic relationship with healthy people. In Crohn’s disease (CD) patients and colitis mice, food acts as an exogenous antigen to hyperactivate CD4+ T cell and relates to high serum IgG levels of intestinal inflammation [25]. Specific
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The significance of bile acid-gut microbiota interaction in CRC

Bile acid-gut microbiota axis in CRC

Bile acid is synthesized in liver and 95% of it is reabsorbed in ileum and recycles into liver to complete enterohepatic circulation. In the presence of gut microbiota, primary bile acid such as CA or chenodeoxycholic acid (CDCA) is converted into secondary bile acid such as DCA or LCA. Bile salt hydrolase (BSH) can hydrolyze the conjugated primary bile acid, which is purified from *Bacteroides fragilis* (B. fragilis), *Bacteroides vulgatus*, *Clostridium perfringens*, *Listeria monocytogenes*, *Lactobacillus* and *Bifidobacterium*. *Clostridium*, *C. scindens*, *C. hiranonis*, *C. hylemonae* (Clostridium cluster XVIa) and *C. sordelli* (C. cluster XI) have the ability of dehydroxylation, thus converting the primary bile acids to secondary bile acids [5]. Meanwhile, bile acid enables the body to regulate the composition of gut microbiota and its derived metabolites. UDCA, tauroursodeoxycholic acid (TUDCA) and glycoursodeoxycholic acid (GU-DCA) normalize Firmicutes/Bacteroidetes ratio, and upregulate the abundance of *Prevotellaceae*, *Clostridium* cluster XIVa, *A. muciniphila* and *Bacteroidia* [34]. In mouse CAC model, *A. muciniphila* and its membrane protein Amuc_1100 reduce the expression of Histone H2AX phosphorylation (γH2AX), cleaved-caspase 3 and Ki67 in colon tissue, which will attenuate double-stranded DNA breaks and inhibit cell proliferation. Moreover, *A. muciniphila* significantly increases cytotoxic T lymphocytes (CTLs) percentage in mesenteric lymph nodes (MLN) and colon, and promotes the expression of TNF-α in CTL though upregulating MHCI and activating the secretion of specific chemokines in tumor cells. These changes are combined to inhibit the tumor formation, reduce tumor number and size and are expected to delay CRC progression [35].

In human, changes in bile acid induce the pro-inflammatory bacteria such as *Mogibacterium* and *Sutterella*, which will aggregate DNA damage and inflammation. Long-term and chronic inflammation means chronic injury of body, making tumor-related genes such as p16, E-cadherin, human mutl homolog 1 (hMLH1), hyperplastic polyposis protein 1 (HPP1), etc.
Figure 1. Bidirectional regulation of bile acid on CRC. The red line and ‘-’ represent inhibiting CRC development, the black line and ‘+’ represent promoting CRC development. CAC: colitis-associated carcinogenesis; HGD: high grade dysplasia; LGD: low-grade dysplasia; CRC: colorectal cancer.
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easy for methylation and silencing, promoting the occurrence of IBD-associated dysplasia and adenoma-carcinoma sequence development \[36, 37\]. Inflammation is a key factor in promoting the occurrence of CRC, which can result in the local intestinal barrier function damage, create a different ecological niche in colon, lead to the outgrowth of bacterial and disrupt the homeostasis and normal metabolic processes \[38\]. The cumulative risk for CRC in UC patients is 2% at 10 years, 8% at 20 years and 18% at 30 years \[39\]. IBD patients, especially IBD-PSC patients have higher incidence of colorectal carcinomas with cumulative risk of 14% at 10 years and 31% at 20 years \[19\]. Therefore, effective inhibition of inflammation is a promising approach to prevent CRC and deserve more researches in the future.

Similar to the relationship between Helicobacter pylori (\(H.\) pylori) and gastric cancer, polyketide synthase (\(pks\))^+ E. coli, enterotoxigenic Bacteroides fragilis (ETBF), E. faecalis and Campylobacter jejuni (C. jejuni) are associated with CRC. Destruction of the epithelial cell barrier causes location-specific bacterial influx or formation of invasive bacterial aggregates, termed as “bacterial biofilms”. Bacterial biofilms mainly consist of \(E.\) coli and \(B.\) fragilis. The former secretes genotoxic colibactin, which induces double-strand breaks, aneuploidy and improper cell division. The latter secretes bacteroides fragilis toxin (BFT), which triggers a pro-carcinogenic multi-step inflammatory cascade by IL-17R, NF-\(\kappa\)B and STAT3 signaling in colonic epithelial cells (CECs). These changes are highly enriched in familial adenomatous polyposis (FAP) patients’ colonic mucosa, indicating the potential role of gut microbiota in the process of polyp-adenoma-CRC.

Pathogenesis of CRC is related to multiple factors and may be involved in disruption of homeostatic, abnormal immune responses and microbiota-derived signals pathways. The imbalance between host and microbiota accompanies with mutation of gene such as APC, KRAS and PIK3CA, and leads to increased cytotoxic bile acid and bacteria and decreased beneficial bacteria, resulting in the sustained epithelial-cell proliferation, resistance to apoptosis and immune evasion. Besides, CRC-associated dysbiosis is associated with neoplasia of CRC and hypermethylation of gene promoters NPY and PENK from the brain-gut system and Wif1 from the Wnt pathway, which may become potential biomarkers for CRC \[38, 40\]. More researches in this field are warranted. Focusing on interaction between bile acid and gut microbiota helps to provide a theoretical basis for the pathogenesis and treatment of CRC.

Bile acid-SCFA-gut microbiota

SCFA is produced from undigested dietary carbohydrate by bacterial fermentation in intestinal lumen.

\(A.\) muciniphila promotes the degradation of mucin into propionic and acetic acid, which will become the substrate for \(Faecalibacterium prausnitzii\) (\(F.\) prausnitzii). \(F.\) prausnitzii is responsible for the production of butyrate in intestine, which can modulate expression of tight junction proteins to minimize para-cellular permeability, activate AMP-activated protein kinase in monolayers, stimulate the production of antimicrobial peptides such as LL-37 and increase the expression of trefoil factors (TFFs). TFFs are mucin-associated peptides and are helpful to maintain and repair intestinal mucosa, thus inhibiting intestinal permeability and inflammation. In turn, butyrate is capable of upregulating expression of mucin 2 (MUC2) on intestinal mucosal surface, reinforcing mucous layer and enhancing protection against luminal pathogens \[41\]. FFA2 (previously GPR43), FFA3 (previously GPR41), GPR109a, and Olfr78 are specific receptors of SCFA. Butyrate is capable of promoting the differentiation of anti-inflammatory IL-10-expressing T cells and inducing apoptosis of intestinal epithelial cells (IECs) by binding to GPR109a, which is of significance to sustain the balance between host and gut microbiota \[41\]. Moreover, butyrate and propionate increase expression of GPR43, inhibit cell proliferation and induce apoptosis by arresting cells in G0/G1 phase, upregulating p21, and decreasing the levels of cyclin D3- and cyclin-dependent kinases (CDKs) 1, 2, thus suppressing CRC progression \[42, 43\].

In CRC cell lines, expressions of GPR109a and GPR43 are suppressed. Loss of these receptors will increase the number and size of colonic polyps and enhance colorectal tumorigenesis in CAC model, characterized by dysregulated inflammatory response, neutrophil migration and increased expression of pro-inflammatory markers such as IL-1\(\beta\) and IL-17\(\alpha\) \[44\]. In CRC
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Figure 2. Bile acid-gut microbiota interaction in CRC. SCFAs: short-chain fatty acids; HIF: hypoxia-inducible factor; pks\(^+\) E. coli: polyketide synthase (pks\(^+\) Escherichia coli; E. faecalis: Enterococcus faecalis; ETBF: Enterotoxigenic Bacteroides fragilis; C. jejuni: Campylobacter jejuni; A. muciniphila: Akkermansia muciniphila; F. prausnitzii: Faecalibacterium prausnitzii.

the proportion of cholinergic enteric neurons, activates vagus nerve and hypothalamus to indirectly affect host appetite and eating behavior, increase insulin sensitivity and glucose tolerance, thus exerting beneficial effect on host metabolism and maintaining homeostasis.

Clostridium butyricum (C. butyricum) is one of the most studied butyrate-producing bacteria. In addition to inhibiting disease progression of IBD, C. butyricum is involved in inhibiting the progression of CRC by regulating the Wnt signaling pathway, gut microbiota and its metabolites. On the one hand, cell experiments confirmed that C. butyricum significantly inhibits proliferation of intestinal tumor cells and promote their apoptosis. On the other hand, animal experiments confirmed that C. butyricum alleviates the increase of pathogenic bacteria such as Desulfovibrio, Odoribacter and Helicobacter, decreases the burden of tumors, reduces the incidence of high-grade dysplasia such as intramucosal carcinoma and inhibits the development of tumors induced by high-fat diet. The anticancer effect of C. butyricum is partly due to altered microbial metabolites. GPR43 and GPR109a specifically recognize SCFA and participate in the inhibition of intestinal inflammation and CRC [48]. Analysis of clinical specimens showed that the expression of GPR43 and GPR109a decreased gradually from human normal colon tissue to adenoma and carcinoma. Gene silencing of GPR43 attenuates the anti-proliferation effect of C. butyricum. However, C. butyrate decreases the level of fecal secondary BA, activates GPR43 and GPR109a and increases cecal SCFA, suggesting that activation of GPR43 and GPR109a plays a key role in the anti-carcinogenic effect of C. butyricum [49] (Figure 2).

Taken together, SCFA have long been thought to provide energy to colonic epithelium and protect from intestinal inflammation [41, 44]. Although some experiments showed that at low

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patients, butyrate producing bacteria such as Eubacterium rectale and Roseburia spp., belonging to Clostridium cluster XIVa and phylum Firmicutes, are decreased [45, 46]. UDCA and its taurine- or glycine-derivatives upregulate the relative abundance of Clostridium cluster XIVa in chronic inflammation animal model and induce regulatory T cells in colon, thus increasing the production of SCFA and inhibiting inflammation-related malignant tumor.

Gradient of O\(_2\) between colonic mucosa lamina propria and gut lumen is steep and pO\(_2\) of colonic epithelial cell is significantly lower than that of other tissues, a condition known as “physiologic hypoxia” [44]. Butyrate, to a less extent of acetate and propionate, promote intestinal epithelial O\(_2\) consumption and maintain the barrier-protective transcription factor hypoxia-inducible factor (HIF) stabilization, thereby enhancing epithelial barrier function, particularly distal gut functions [47].

Brain-gut axis is composed of the central nervous system, enteric nervous system and a variety of neurons, involving in signal transduction between brain and gut. Butyrate enhances

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concentrations (1-10 mM), butyrate strengthens epithelial barrier function, whereas at high concentrations (50-100 mM), it shows no beneficial effects [50]. Given the relationship between SCFA and intestinal barrier, immune response and metabolism, study of relationship between SCFA, bile acid and gut microbiota is helpful to further elucidate the bidirectional regulation of bile acid on CRC and provide new ideas for the future treatment of CRC.

**Limitations of bile acid application and future directions**

Bile acid is often used as a treatment drug for PSC and intrahepatic cholestasis of pregnancy and so on. In CRC, bile acid exerts bidirectional regulation on host by interacting with gut microbiota.

Although some studies have shown that bile acid has a certain inhibitory effect on intestinal inflammation and the formation and development of tumor, its carcinogenic effect on CRC affects the evaluation of its efficacy and limits its extensive clinical application. However, the diversity of its effects also means that it has multiple potentials. By targeting the regulation of abnormal metabolites and signaling pathways and immune responses, it is expected to reduce its carcinogenic effect and play its anti-cancer effect as much as possible. This will help to provide theoretical basis for its future application in CRC or combined application with other drugs to treat diseases.

**Conclusion**

CRC is a heterogeneous disease of intestinal epithelium, characterized by gene mutation accumulations, dysregulated immune responses and dysbiosis. Bile acid may inhibit the course of CRC to some extent by interacting with gut microbiota. Gene, immune, metabolism and diet are also involved in the interplay and affect tumor progression. Study of bidirectional regulation of bile acid and its interaction with gut microbiota is helpful to better understand CRC pathogenesis and expect to be a new option for the treatment of CRC.

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**Disclosure of conflict of interest**

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