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Fecal microbiota transplantation in cancer management: Current status and perspectives

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The human gut is home to a large and diverse microbial community, comprising about 1,000 bacterial species. The gut microbiota exists in a symbiotic relationship with its host, playing a decisive role in the host's nutrition, immunity and metabolism. Accumulating studies have revealed the associations between gut dysbiosis or some special bacteria and various cancers. Emerging data suggest that gut microbiota can modulate the effectiveness of cancer therapies, especially immunotherapy. Manipulating the microbial populations with therapeutic intent has become a hot topic of cancer research, and the most dramatic manipulation of gut microbiota refers to fecal microbiota transplantation (FMT) from healthy individuals to patients. FMT has demonstrated remarkable clinical efficacy against *Clostridium difficile* infection (CDI) and it is highly recommended for the treatment of recurrent or refractory CDI. Lately, interest is growing in the therapeutic potential of FMT for other diseases, including cancers. We briefly reviewed the current researches about gut microbiota and its link to cancer, and then summarized the recent preclinical and clinical evidence to indicate the potential of FMT in cancer management as well as cancer-treatment associated complications. We also presented the rationale of FMT for cancer management such as reconstruction of intestinal microbiota, amelioration of bile acid metabolism, and modulation of immunotherapy efficacy. This article would help to better understand this new therapeutic approach for cancer patients by targeting gut microbiota.

Key words: gut microbiota, dysbiosis, cancer, fecal microbiota transplantation, therapy

Abbreviations: CDI: *Clostridium difficile* infection; CRC: colorectal cancer; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; FMT: fecal microbiota transplantation; *Fn*: *Fusobacterium nucleatum*; GVHD: graft-*vs*.-host disease; HCC: hepatocellular carcinoma; HSCT: hematopoietic stem cell transplantation; PD-1: programmed cell death protein 1; PDAC: pancreatic ductal adenocarcinoma; PD-L1: programmed death ligand 1; *Sgg*: *Streptococcus gallolyticus subsp. Gallolyticus*; TLRs: Toll-like receptors

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Introduction

The human intestinal tract is inhabited by numerous microbes, and the number of microbial cells is roughly equivalent to that of cells in human body.[1] The human intestine contains about 1,000 different species of known bacteria with the largest number of bacteria in colon.[2] The bacterial populations inhabiting the gut differ greatly between individuals,[2] depending on host specificities (such as genetics and lifestyle).

In recent decades, understanding of the role that intestinal microbial community plays in health and disease has increased.[3,4] The intestinal microbial community in a state of delicate balance is now widely recognized to maintain health. However, as the balance can be disrupted by various factors including host genetics, diet, antibiotics and stress, altered microorganisms potentially initiate and perpetuate different disorders.[5] Various studies have shown that microbial alternations, characterized by a marked increase in the numbers of pathogens and a relative decrease in levels of beneficial bacteria, are connected with the development of gastrointestinal and extra-gastrointestinal cancers.[6–13]

Altering the gut microbiota is expected as a novel method to deal with diseases associated with intestinal dysbiosis. Potential routes to target intestinal microbiota community include diet, probiotics, prebiotics, antibiotics and fecal microbiota transplantation (FMT). FMT is defined as the transplantation of gut microbiota from healthy donors to sick patients *via* the upper or lower gastrointestinal route to restore intestinal microbial diversity.[14,15] FMT is recognized as the most innovative and dramatic method due to its ability to alter the

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recipients' gut microbiota. The utilization of feces for the treatment of food poisoning or severe diarrhea was firstly recorded by a well-known medical expert named Ge Hong approximately 1,700 years ago.[16] FMT was firstly reported to treat severe pseudomembranous enterocolitis by Eiseman in 1958.[17] Nevertheless, this practice was less used until the first documented case of *Clostridium difficile* infection (CDI) treated with FMT was reported in 1983 by Schwan.[18] Currently, FMT has been approved as a clinical method for treating recurrent CDI by 2013 guidelines[19] and its clinical effectiveness has reached approximately 90%.[20] Moreover, accumulating data indicate that FMT proves beneficial for the treatment of inflammatory bowel diseases and intractable functional constipation, etc.[21,22] In addition, the observed intestinal dysbiosis in cancer leads to increasing interests in the potential of FMT for the management of cancer.

Fecal donors are either close relatives, family members or unrelated individuals. However, where possible, fecal material is best sourced from a healthy unrelated individual, from a centralized stool bank.[23] To eliminate the risk of inadvertently transmitting infection, donors in preparation of FMT should be screened according to an established protocol.[24] With regard to methods of preserving fecal materials, the frozen fecal material has the advantage of more convenient management.[25] However, the bacterial diversity of frozen product seems lower than that of fresh material.[26] In a recent double-blind study of patients with CDI, the frozen fecal product had a lower efficacy compared to fresh material.[27] As well as differences in recipient preparation methods, the routes of administration are also various. Fecal microbiota can be delivered *via* capsule, nasogastric tube, nasoduodenal tube, enema, or colonoscopy.[28] Although endoscopic administration allows direct evaluation of intestinal mucosa, oral administration is accepted easily by patients due to higher satisfaction.[29] Retention enema is cheap and safe, but it might be hard to retain the donor microbiota.[30] The optimum route of administration has not yet been determined. A European consensus conference on FMT published in *Gut* strongly recommended the implementation of FMT centers,[31] while Terveer *et al.* deemed that a centralized stool bank could ensure the safety of fecal materials, and permit the rest of the FMT procedures in local hospitals.[32]

In this review, we focused on gut microbiota in various cancers. We then summarized the current preclinical and clinical studies on the use of FMT for gastrointestinal and non-gastrointestinal cancers as well as cancer treatment-associated complications including CDI and radiation enteritis (Table 1).

Gut Microbiota and Cancer

During the past several years, the involvement of gut microbiota in carcinogenesis has been increasing recognized.[9,33] Microbial dysbiosis and individual bacteria in the gut can induce carcinoma or promote cancer process by activating tumorigenic pathway, inducing inflammation and damaging host DNA[34,35] (Fig. 1). Several bacteria possess or produce proteins that promote the separation of β-catenin from E-cadherin, activating β-catenin signal pathway involved in carcinogenesis. Intestinal dysbiosis leads to a decrease in the production of bacteria-derived short-chain fatty acids. Intestinal dysbiosis exerts pro-inflammatory effects, *via* microorganism-associated molecular patterns by Toll-like receptors (TLRs), increasing the cells' production of pro-inflammatory factors, thereby increasing carcinogenesis. Beyond inducing inflammation, many bacteria also have the ability to damage DNA through releasing specific metabolites, which in turn promote cancer progression. Surprisingly, specific microbiota species modulate the efficacy of cancer therapy,[36] markedly influencing the clinical outcome of cancer patients. Hence, a better knowledge of the link between intestinal bacteria and cancer can provide opportunities to develop promising therapeutic and diagnostic strategies.

Gut dysbiosis and cancer development

The alterations in gut microbiota composition have been implicated in the initiation and development of cancer of various tissues, including gastric cancer, colorectal cancer (CRC), hepatocellular carcinoma (HCC), pancreatic cancer, breast cancer, and melanoma. Recent studies have described the specific changes in the gut bacterial community in patients with cancers (such as gastric cancer or CRC) in comparison with healthy individuals.[37,38] The fecal microbiota from patients with CRC promoted tumorigenesis in germ-free or conventional mice given a carcinogen,[39] which showed the carcinogenic properties of the CRC microbiota. Accumulating epidemiological evidence supports the opinion that long-term antibiotic exposures, known to change the composition and decrease the diversity of gut microbiota,[40] increase the risk of CRC,[41–44] as well as gastric, pancreatic, lung, breast and prostate cancers.[45] Consistent with this, long-term antibiotic use was highly correlated with increased colorectal tumor progression in the $Apc^{Min/+}$ mouse, a genetic model for human adenomatous polyposis.[46] However, there is conflicting data about the association between antibiotics and risk of cancer. Oral administration of metronidazole could reduce *Fusobacterium* load and colorectal tumor growth in mice bearing a colon cancer xenograft.[47] Moreover, antibiotic use could clear biofilms and eliminate microbial sulfide, and thereby protect the colon mucous barrier and prevent epithelial hyperproliferation.[48,49] Additionally, several studies have suggested that depletion of the gut microbiota upon exposure to an antibiotic cocktail could block intestinal tumorigenesis.[50–52] It is possible that different antibiotic exposures (differ in dose or course) and subjects may lead to diverse variations in microbial community, which could result in distinct disease outcomes (Supporting Information, Table S1). Further investigations are required to elucidate the impact of antibiotic exposures on outcomes in cancer patients and its underlying mechanisms. With the deepening comprehension of gut dysbiosis, interest is growing rapidly worldwide in the application of microbiota-target therapy for cancer.

Table 1. Summary of studies of fecal microbiota transplantation in cancer management

Cancers and treatment-associated complications	Ref.	Publication year	Study type
Colorectal cancer	Rosshart *et al*.[91]	2017	Experimental study
	Wong *et al*.[39]	2017	Experimental study
	Our study[52]	2017	Experimental study
Chronic liver disease			
Nonalcoholic steatohepatitis	De *et al*.[95]	2014	Experimental study
	Zhou *et al*.[100]	2017	Experimental study
Alcoholic hepatitis	Llopis *et al*.[96]	2016	Experimental study
	Philips *et al*.[103]	2017	Case report
	Ferrere *et al*.[101]	2017	Experimental study
	Philips *et al*.[102]	2017	Experimental study
Chemical-induced liver injury	Qin *et al*.[97]	2017	Experimental study
Chronic hepatitis B	Ren *et al*.[104]	2017	Experimental study
Liver cirrhosis	Bajaj *et al*.[105]	2018	RCT
Hepatic encephalopathy	Kao *et al*.[107]	2016	Case report
	Wang *et al*.[106]	2017	Experimental study
	Bajaj *et al*.[108]	2017	RCT
Hepatocellular carcinoma	Ma *et al*.[93]	2018	Experimental study
Pancreatic cancer	Pushalkar *et al*.[114]	2018	Experimental study
Melanoma	Gopalakrishnan *et al*.[71]	2018	Experimental study
Cancer treatment-associated complications			
Recurrent CDI	Neemann *et al*.[127]	2012	Case report
	Kelly *et al*.[123]	2014	Observational study
	Blackburn *et al*.[124]	2015	Case report
	Trubiano *et al*.[125]	2015	Case report
	Mittal *et al*.[126]	2015	Case report
	de Castro *et al*.[128]	2015	Case report
	Webb *et al*.[129]	2016	Case report
	Innes *et al*.[130]	2017	Case report
	Hefazi *et al*.[122]	2017	Observational study
Radiation enteritis	Cui *et al*.[132]	2017	Experimental study
	Gerassy-Vainberg *et al*.[131]	2018	Experimental study
Graft-*versus*-host disease	Kakihana *et al*.[135]	2016	Case report

Abbreviations: RCT, Randomized controlled trial; CDI, *Clostridium difficile* infection.

Special microbial pathogens in cancer

It has been estimated that some microorganisms as etiological factors, such as *Human papillomavirus*, *Helicobacter pylori* (*H. pylori*) and *Hepatitis B virus*, account for about 20% of total cancers worldwide.[53] Several bacterial species and their tumor-promoting mechanisms have been investigated mostly on cell and animal levels, including production of toxic metabolites, alteration of intestinal microenvironment, induction of tumorigenic signaling pathways (Supporting Information, Table S2). For example, *H. pylori* is well known to contribute to the development of chronic gastritis and gastric carcinogenesis by secreting virulence factors and activating various tumor-promoting signaling pathways.[54–58] Enterotoxigenic *Bacteroides fragilis*, the producer of *Bacteroides fragilis* toxin, can induce intestinal inflammation and DNA damage, which participates in the pathogenesis of CRC.[59] *Streptococcus gallolyticus subsp. gallolyticus* (*Sgg*), a Gram-positive, opportunistic pathogen, is present in most colon tumor tissue compared to normal tissues in CRC patients.[60] *Sgg* has also been shown to promote the development of colon tumor *via* the β-catenin signaling pathway in mice given a carcinogen.[61] Pathogenic *Escherichia coli* (*E. coli*) can produce many toxins including cyclomodulin, which is involved in tumorigenesis.[62] Lately, gram-negative oral commensal *Fusobacterium nucleatum* (*Fn*), which is enriched in colon tumor tissues compared to adjacent healthy tissues, has been reported to promote proliferation and invasion ability of tumor cells.[63–65] Additionally, *Fn* induces cancer cell autophagy, thereby increasing chemotherapeutic drug resistance and tumor recurrence rate.[66]

The significant difference in gut microbiota composition between cancer patients and healthy individuals demonstrates diagnostic and prognostic potentials of special microbial pathogens in cancer. For examples, a significant stepwise increase of *Fn* abundance was found in healthy controls, colorectal adenoma patients and CRC patients, indicating its potential application

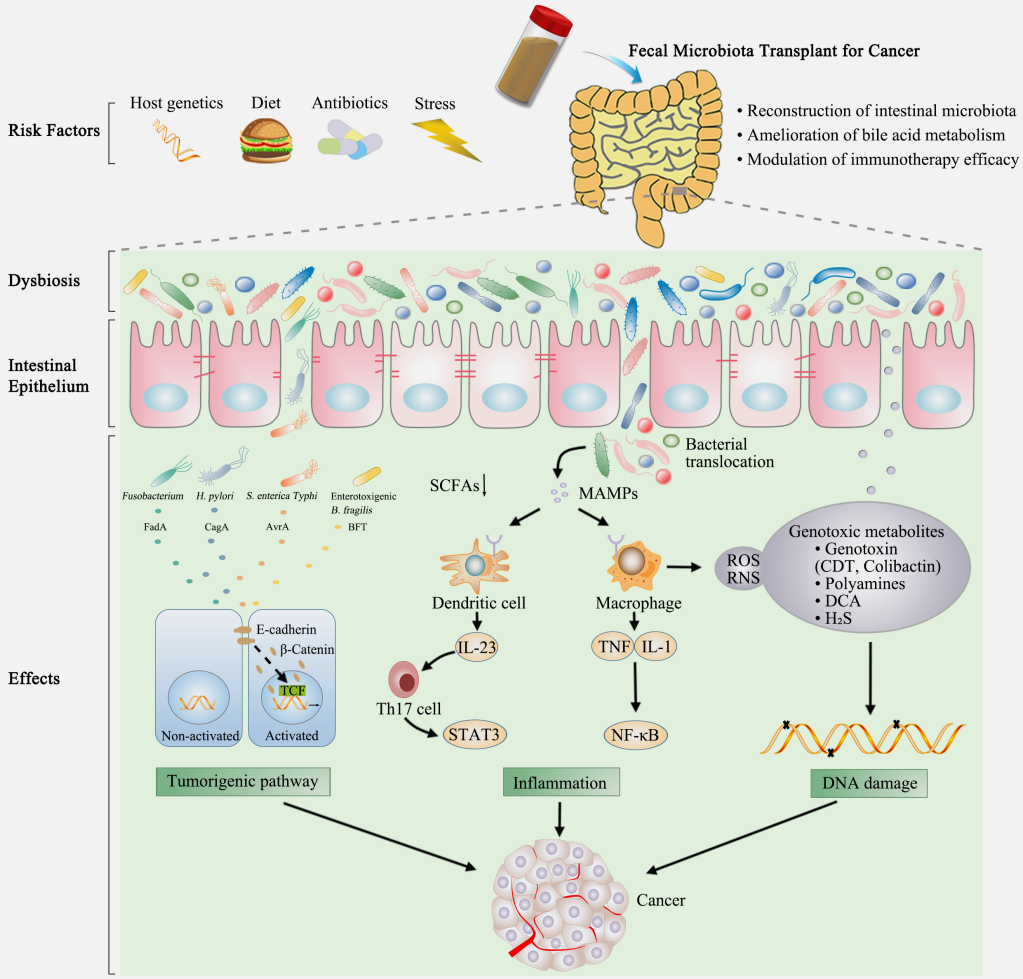

Figure 1. Management of cancer by fecal microbiota transplant. FMT represents a potential therapeutic strategy for cancer by reconstruction of intestinal microbiota, amelioration of bile acid metabolism and modulation of immunotherapy efficacy. Various factors such as host genetics, diet, antibiotics and stress could lead to alterations of gut microbiota, named as gut dysbiosis. Microbial dysbiosis and special bacteria in the gut are capable of affecting cancer development and progression *via* activating tumorigenic pathway, inducing inflammation and damaging host DNA. Special bacterial products, such as FadA toxin from *Fusobacterium nucleatum*, CagA protein from *Helicobacter pylori*, AvrA protein from *S. enterica* Typhi, and BFT from Enterotoxigenic *Bacteroides fragilis* can promote the separation of β-catenin from E-cadherin, which can trigger β-catenin activation and contribute to tumorigenesis. The beneficial component in bacterial metabolites, such as SCFAs, is also decreased in microbial dysbiosis. Intestinal dysbiosis may be conducive to bacterial translocation, exerting pro-inflammatory effects, which is mediated by MAMPs that activate TLRs in macrophages and dendritic cells. TLR signaling promotes the expression of the pro-inflammatory factors, including IL-23, TNF and IL-1, thereby promoting carcinogenesis. Several microbial metabolites can directly or indirectly damage host DNA, fueling carcinogenesis. Special microbial toxins (CDT and colibactin) could directly induce DNA damage. Furthermore, gut bacteria also damage DNA indirectly *via* polyamines, DCA, ROS, RNS and H_2S. FMT, fecal microbiota transplantation; BFT, *Bacteroides fragilis* toxin; SCFAs, short-chain fatty acids; MAMP, microbe-associated molecular pattern; TLR, Toll-like receptor; IL-23, interleukin 23; TNF, tumor necrosis factor; IL-1, interleukin; Th17, T helper 17; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor-κB; CDT, cytolethal distending toxins; DCA, deoxycholic acid; H_2S, hydrogen sulphide; RNS, reactive nitrogen species; ROS, reactive oxygen species. [Color figure can be viewed at wileyonlinelibrary.com]

value in early diagnosis of CRC.[67] Combining the abundance of *Fn* and fecal immunochemical test could improve the accuracy and sensitivity in diagnosis of CRC and advanced adenoma.[67,68] In addition to the diagnostic utility, the amount of *Fn* in CRC tissue is associated with patient survival. Collectively, a better understanding of how special microbial pathogens elicit specific carcinogenesis may uncover valuable biomarkers for diagnosing and prognosticating cancer.

Gut microbiota and cancer therapy

Gut microbiota could influence cancer therapy efficacy. In 2013, Viaud *et al.* reported that gut microbiota modulated the therapeutic effect of the anti-cancer immunomodulatory agent cyclophosphamide.[69] Subcutaneous cancer-bearing mice which were germ-free or given antibiotics therapy to kill gram-positive bacteria showed resistant to cyclophosphamide.[69] Two bacterial species, *Enterococcus hirae* and *Barnesiella intestinihominis*, were identified to potentiate the antitumor efficacy of cyclophosphamide through engagement of immune responses.[70]

Several studies using melanoma-bearing mice showed that the effectiveness of programmed cell death protein 1 (PD-1) inhibitor was diminished under aseptic conditions,[71] and improved effectiveness was observed in the presence of *Bifidobacterium*, which activated antigen-presenting cells, thus promoting activated CD8+ T cells accumulation in the tumor microenvironment.[72] MCA205 (mouse fibrosarcoma of C57BL background) sarcoma growth was controlled by anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA -4) therapy in specific pathogen free laboratory mice, compared to germ-free or antibiotic-treated mice.[73] These studies highlight the impact of the intestinal microbiota on responses to cancer immunotherapy in mice.

Lately, corroborating these experimental results, clinical outcomes such as survival time to anti-PD-1 monoclonal antibodies were found to positively correlate with the relative abundance of *Akkermansia*, one of the most abundant bacteria in the ileum of healthy individuals.[74] Microbiome encompasses microbiota genomes, microbial products and host environment.[75] Transfer of the gut microbiome from cancer patients who responded to immunotherapy and oral supplementation of *Akkermansia* improved the efficacy of immunotherapy.[74] Together, it is tempting to speculate that FMT is beneficial for the treatment of cancer.

FMT as a Possible Therapy for Various Type of Cancers and Cancer Treatment-Associated Complications

FMT for digestive system cancers

Gastrointestinal cancers. Carcinogenesis of gastric cancers is associated with *H. pylori* and some oral microbiota including *Fn*, *Parvimonas micra* and *Peptostreptococcus stomatis.*[76] Significant enrichment of *Peptostreptococcus stomatis*, *Parvimonas micra*, *Streptococcus anginosus*, *Dialister pneumosintes*, *Slackia exigua,*[38] *Clostridium colicanis* and *Fn*[77] and depletion of *Helicobacterium*[78] was observed in gastric cancer, and alterations in bacterial diversity and abundance in patients with gastric cancer revealed a dysbiotic microbial community with prediction potential.[79] Recently, incremental data has demonstrated that eradication treatment for *H. pylori* could reduce the risk of gastric cancer.[80,81] Collectively, these studies indicate that gastric microbiota is involved in gastric carcinogenesis. With enormous microorganism at close proximity to the colonic epithelial cells, the involvement of gut microbiota in colorectal carcinogenesis is becoming clear. Indeed, some bacterial species can trigger the occurrence of CRC through toxic substance exposure, chronic inflammation, mucosal barrier injury and bacterial translocation. Pathogenic bacteria species, such as enterotoxigenic *Bacteroides fragilis*, can confer protumorigenic traits *via* producing harmful substances.[82–84] Moreover, clinical studies reported significant shifts in intestinal microbiota composition between healthy individuals and those afflicted with CRC, showing a CRC-specific bacterial signature.[37,85] Some bacteria (such as *Lactobacillus*, *Bifidobacterium*, etc.) were diminished, while others (such as *Staphylococcaceae*, *Fusobacteria*, *Peptostreptococcus anaerobius*, etc.) were augmented in stool samples from patients with CRC *vs.* healthy individuals. Analysis of fecal microbiota as a noninvasive tool might be used to improve detection accuracy of early CRC.[86]

There are several evidences that support a protective role of probiotics against CRC. As known butyrate producers, *Clostridium butyricum* and *Bacillus subtilis* could inhibit DMH-induced colonic tumor in mice.[87] Notably, another probiotic, *Lactobacillus casei* strain BL23 not only inhibited CRC in mice, but also counteracted gut dysbiosis induced by CRC.[88] Additionally, recent clinical studies established that oral *Bifidobacterium* triple viable probiotics could improve gut dysbiosis and combat small intestinal bacterial overgrowth in CRC patients.[89,90]

Our team identified the role of intestinal dysbiosis induced by deoxycholic acid (a carcinogenic secondary bile acid) in the development of CRC. We found that the transfer of feces from deoxycholic acid-treated mice increased intestinal tumor development compared to untreated donor.[52] Interestingly, the result has been verified in patients in a recent study, and the fecal microbiota from patients with CRC promoted intestinal tumor formation and lowered microbial abundance in germ-free and conventional mice given a carcinogen.[39] Moreover, Rosshart *et al.* reported that laboratory mice transplanted with intestinal microbiomes from wild mice showed better resistance to CRC and amelioration of inflammation, compared to control mice of their own bacteria,[91] supporting the assumption that FMT could harbor a potential therapeutic ability for CRC.

Hepatocellular carcinoma. The liver is exposed to intestinal microbiota through the portal vein which delivers gut-derived bacterial products or toxins, such as lipopolysaccharide and deoxycholic acid.[6,92] The close structural and functional interaction between the gut and the liver is defined as the gut-liver axis. Liver diseases are often associated with intestinal dysbiosis, and it has been shown that gut bacterial metabolites could promote the development of chronic liver disease and HCC through gut-liver axis.[93,94]

Alteration of intestinal microbiota has been reported in liver disease, but the extent to which it is a cause is unknown. Microbiota transplantation from mice with high-fat diet-induced chronic liver damage revealed more liver injury in recipient mice.[95] The stool from patients with severe alcoholic

hepatitis increased the susceptibility to chronic alcoholic liver disease in mice.[96] Microbial dysbiosis after penicillin or dextran sulfate sodium in rats aggravated hepatotoxicity of recipient mice.[97] Moreover, colonization of *Clostridium* species, which could influence the metabolism of bile acids, increased liver tumor growth in mice with gram-positive bacteria removed.[93] These data provide direct evidence that microbial dysbiosis could directly contribute to liver disease.

There are several clinical studies regarding the use of probiotics as a novel and effective approach to treat or prevent chronic liver disease and HCC. Probiotic VSL#3, a combination of *Bifidobacteria*, *lactobacilli* and *Streptococcus thermophilus*, could short inpatient time for patients with liver cirrhosis and hepatic encephalopathy.[98] A randomized controlled multicenter study involving 117 alcoholic hepatitis patients found that those who received probiotics treatment with *Lactobacillus subtilis* and *Streptococcus faecium* had lower level of serum lipopolysaccharide, compared to the placebo group.[99]

More recently, extensive research supports that FMT is showing promise as a therapy to control liver disease. FMT improved high-fat diet-induced liver injury and lipid metabolism along with increased gut microbiota diversity in mice.[100] FMT from donor mice resistant to alcoholic liver disease could prevent alcohol-induced liver injury.[101] Moreover, FMT has already been used in human with chronic liver disease. A recent pilot study of patients with severe alcoholic hepatitis showed that FMT was associated with increased survival and resolved ascite.[102] Philips *et al.* reported a case of a young male patient with corticosteroid nonresponsive severe alcoholic hepatitis in 2017.[103] FMT led to rapid amelioration of appetite and hyperbilirubinemia. Notably, FMT was performed in 18 patients with persistent positive HBeAg.[104] FMT was effective for these patients *via* inducing HBeAg clearance, suggesting that regulating intestinal microbiota might be beneficial to chronic hepatitis B treatment. A Phase I clinical trial demonstrated that FMT restored antibiotic-induced microbial dysbiosis in patients with advanced liver cirrhosis.[105] Even more, the effect of FMT on hepatic encephalopathy has been confirmed in both animal models and human beings. FMT alleviated cognitive function and prevented hepatic necrosis in animal models, thereby triggering improvement of hepatic encephalopathy.[106] Kao *et al.* reported a significant improvement in serum ammonia and quality of life in a patient with hepatic encephalopathy after performing FMT.[107] Bajaj *et al.* conducted a randomized clinical trial, which suggested that FMT has the potential to improve cognition and reduce hospitalizations in hepatic encephalopathy patients.[108] Given the success of treating chronic liver disease, the benefit of FMT in patients with HCC deserves attention.

Pancreatic cancer. Recent studies have demonstrated that microbiota influences the development and treatment of pancreatic cancer.[109] Evidence in mouse model manifested that lipopolysaccharide, which is generated from many gram-negative bacteria, could promote pancreatic cancer formation *via* activating TLR4 in immune cells.[110] In a recently published study, 76% of subjects were positive for intratumor bacteria in 113 humans with pancreatic ductal adenocarcinoma (PDAC).[111] Some of these detected bacteria including *Gammaproteobacteria* could promote resistance to gemcitabine, a chemotherapeutic drug commonly used for PDAC, while antibiotic ciprofloxacin was able to abrogate the resistance.

Previous studies have shown the variation of oral microbial composition between healthy and pancreatic cancer individuals. Among pancreatic cancer groups, significant increases were noted in *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, and significant decreases were observed in *phylum Fusobacteria* and genus *Leptotrichia*, suggesting the potential of oral microbiota to serve as a noninvasive and specific clinical diagnostic marker for pancreatic cancer.[112] Moreover, the high abundance of *Fusobacterium* species in pancreatic cancer tissue was independently correlated with a worse prognosis,[113] indicating that Fusobacterium species might become a promising prognostic parameter of pancreatic cancer. The transfer of the microbiota from mice with PDAC, but not healthy mice, accelerated tumor progression in germ-free mice.[114] Taken together, these studies revealed that microbiota-based treatment might be useful to manage pancreatic cancer.

FMT for nondigestive system cancers

Breast cancer. Hill *et al.* first proposed a hypothesis about gut microbiota and the etiology of breast cancer in 1971, considering the similarity of colon and breast cancer in epidemiologic characteristics.[115] By now, studies on the direct relationship between gut microbiota and breast cancer are rather limited. Goedert *et al.* analyzed differences between 48 pretreatment postmenopausal breast cancer patients and 48 healthy controls.[116] Compared to controls, patients had significantly reduced alpha diversity and alterations in the composition of fecal microbiota. Studies have been dedicated to possible mechanisms, such as estrogen metabolism, immune regulation, obesity and so forth.[117] Evidence from animal experiments suggests that modulation of the gut microbiota by probiotics can provide protection against breast cancer. For example, oral supplement with *Lactobacillus acidophilus* can delay the development of breast cancer by regulating antitumor immune response.[118] Further work is needed to elaborate the mechanism, and thus to manipulate gut microbiota with regards to management of breast cancer.

Melanoma. Recent evidence demonstrates that gut microbiota has implications for the progression and treatment of melanoma. Melanoma growth and its response to anti-programmed death ligand 1 (PD-L1) immunotherapy in two mouse facilities (JAX and TAC) harboring distinct gut microbial compositions were remarkably different.[72] Through genomic analyses of the gut microbiota, *Bifidobacterium* was

identified to facilitate the effects of PD-L1 treatment.[72] Lately, a study of 39 metastatic melanoma patients receiving immune checkpoint therapy also showed that there was a significant correlation between the content of microorganism and the response of immunotherapy.[119] In the responders to cancer immunotherapy, *Bacteroides thetaiotaomicron*, *Faecalibacterium prausnitzii* and *Holdemania filiformis* were rich in their gut.[119] The transfer of feces harvested from responding melanoma patients into mice established that FMT could enhance the effectiveness of immunotherapy to optimize the current therapies.[71] A clinical study is testing the effect of FMT from PD-1 responders into intestinal tracts of nonresponders in melanoma.[120] Thus, FMT seems to be promising in enhancing antitumor immunity in melanoma patients by transferring a favorable gut microbiota.

FMT for cancer treatment-associated complications

Clostridium difficile infection. *Clostridium difficile* is the most common cause of antibiotic-associated diarrhea, leading to high morbidity and mortality in cancer patients. Both primary and recurrent CDI are not uncommon in patients with cancer owing to the fact that chemotherapy, frequent use of broad-spectrum antibiotics, prolonged hospitalization, immunodepression and other factors can lead to the damage of normal gut microbiota.[121] Obviously, FMT is an effective and acceptable procedure for the treatment of recurrent CDI and now recommended in clinical use. Recent research has demonstrated the effectiveness of FMT for clinical cure of recurrent CDI approximately 90%.[20] Apart from the successful restoration of microbial diversity and bacterial metabolites, the regulation of bile acid metabolism is also one of the mechanisms of FMT for CDI.[24]

Although long-term safety data are lacking, the benefit of FMT on CDI in cancer patients has been confirmed by clinical studies and case reports. Hefazi *et al.* investigated the influence of FMT for recurrent CDI in 23 cancer patients (mainly hematologic cancer) receiving cancer chemotherapeutic agents. It is compelling to observe that the effective rate was 86% without serious adverse reactions or infectious complications.[122] Kelly *et al.* analyzed 80 immunocompromised patients who underwent FMT, and found that no infectious complications resulted from FMT.[123] In addition, several clinical trials have been conducted and published about the successful utilization of FMT for diarrhea caused by *Clostridium difficile* in patients with T-cell lymphocytic leukemia[124] or B-cell lymphoma.[125,126] Hematopoietic stem cell transplantation (HSCT) is the most effective and promising procedure for treating hematological malignancy. To our knowledge, the first case of successful application of FMT for severe CDI that was refractory to conventional treatment with antibiotics in an HSCT patient was reported in 2012.[127] Then two simple case reports were published about FMT as the management of CDI refractory to conventional therapy,[128,129] showing that this approach is safe and effective in CDI after HSCT without infectious complications and other adverse effects while conventional therapy fails. The first case that before preparing for HSCT, FMT effectively solved the problem of pathogenic bacteria infection was reported in 2017. A male patient suffered from Philadelphia-positive acute lymphoblastic leukemia and developed a severe infection (β-lactamase-producing *E. coli*, *Clostridium difficile* and carbapenemase-producing *Enterobacteriaceae*) before preparing for HSCT. After receiving FMT, his infection symptoms improved.[130]

Radiation enteritis. Radiotherapy is one of the most successful cancer therapies, but it may give rise to severe tissue damage that limits its use. Small intestine epithelium has high sensitivity to radiation and is the major site of radiation-induced injury due to frequent intestinal epithelial turnover.[131] A shift in intestinal microbiota composition after radiotherapy was observed in mice.[131,132] FMT from irradiated mice to germ-free mice exposed to radiation resulted in more severe radiation damage, compared to mice transplanted with naïve microbiota.[131] Interestingly, transplantation of fecal microbiota from healthy mice significantly alleviated radiation-induced gastrointestinal syndrome and improved the survival rate of irradiated mice.[132] Therefore, FMT might be employed as a radioprotector in tumor radiotherapy to improve the prognosis.[132]

Graft-versus-host disease. In allogeneic HSCT, donor T cells attack host healthy tissues, resulting in graft-*vs.*-host disease (GVHD), which is the main cause of mortality associated with HSCT.[133] A clinical study identified intestinal bacterial diversity as a new independent prognostic factor in allogeneic HSCT.[134] Allogeneic HSCT led to impaired gut microbiota with decreased diversity, and patients with higher intestinal diversity had a better prognosis and prolonged survival time than patients with lower diversity.[134] Successfully applying FMT to stem cell transplantation patients with intestinal acute GVHD was first reported by Kakihana in 2016.[135] Of the four patients who underwent FMT, three achieved complete response, and one had a partial response. Targeted restoration of gut microbiota *via* FMT may present a novel ecological strategy for managing GVHD.

Safety of FMT

FMT has been designated as a biological drug by the U.S. Food and Drug Administration, and doctors need to submit an investigational new drug application so as to obtain permission to implement FMT for treating any disease or condition other than recurrent CDI.[136] Offering FMT treatment is requested strictly, while the majority of existing literature indicating that it is not allowed in clinics without ethics approval. Because of the unidentified composition and pathogenicity of fecal bacteria, the safety of FMT remains controversial.[137] Moreover, as an emerging treatment, FMT has not

been applied for a long time, so it lacks a long-term safety investigation. Consequently, it is quite indispensable to closely follow the patients after FMT and carefully recorded their condition. Our team conducted a systematic review among 1,089 patients receiving FMT in a total of 50 selected publications and found that serious side effects, such as death and virus infections, were not rare.[138] Two cases of norovirus gastroenteritis were reported in FMT recipients, though the donor was innocent of the transmission.[139] Although there are some encouraging success cases and clinical studies, the quality of evidence of FMT in cancer management remains generally low. High quality clinical data are still required to further investigate whether could be employed as a safe therapeutic intervention against cancer.

Conclusion and Perspective

The role of the intestinal microbiota and its relationship to carcinogenesis provide an unprecedented opportunity to explore new diagnostic and therapeutic applications for cancers. Strategically FMT is the most direct method to change the composition of gut microbiota. Case reports and series reveal the potential of FMT in alleviating various cancers linked to intestinal dysbiosis and cancer treatment-associated complications. Additionally, FMT could enhance the efficacy of cancer immunotherapy, thus remarkably affect clinical outcomes. However, FMT has not been clearly studied in cancer management and large-sample randomized controlled studies are urgently required to delineate the validity of FMT, especially focus on the long-term consequences. With the rapid progress of gut microbiology, FMT might become a promising therapeutic strategy for cancers in the near future.

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