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REVIEW

Fecal microbiota transplantation broadening its application beyond intestinal disorders

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Abstract

Intestinal dysbiosis is now known to be a complication in a myriad of diseases. Fecal microbiota transplantation (FMT), as a microbiota-target therapy, is arguably very effective for curing *Clostridium difficile* infection and has good outcomes in other intestinal diseases. New insights have raised an interest in FMT for the management of extra-intestinal disorders associated with gut microbiota. This review shows that it is an exciting time in the burgeoning science of FMT application in previously unexpected areas, including metabolic diseases, neuropsychiatric disorders, autoimmune diseases, allergic disorders, and tumors. A randomized controlled trial was conducted on FMT in metabolic syndrome by infusing microbiota from lean donors or from self-collected feces, with the resultant findings showing that the lean donor feces group displayed increased insulin sensitivity, along with increased levels of butyrate-producing intestinal microbiota. Case reports of FMT have also shown favorable outcomes in Parkinson's disease, multiple sclerosis, myoclonus dystonia, chronic fatigue syndrome, and idiopathic thrombocytopenic purpura. FMT is a promising approach in the manipulation of the intestinal microbiota and has potential applications in a variety of extra-intestinal conditions associated with intestinal dysbiosis.

Key words: Fecal microbiota transplantation; Intestinal microbiota; Dysbiosis; Extra-intestinal disorders; Therapy

Core tip: Fecal microbiota transplantation (FMT) achieved a successful cure rate in recurrent *Clostridium difficile* infection. Although there is a deficiency of randomized controlled trials, the present review reveals

that FMT could be a promising rescue therapy in extra-intestinal disorders associated with gut microbiota, including metabolic diseases, neuropsychiatric disorders, autoimmune diseases, allergic disorders, and tumors.

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INTRODUCTION

The human intestinal tract is home to up to 10^{14} microbes, outnumbering human cells within our bodies by tenfold[1,2]. The number and diversity of bacteria differ according to the different anatomical areas, ranging from the proximal to the distal gastrointestinal tract, with the colon harboring most of the intestinal microbiota[3]. Such an environment developed by host-bacteria associations is termed as being mutualistic. Four predominant bacterial phyla are identified in the human intestine: *Bacteroidetes, Firmicutes, Actinobacteria*, and *Proteobacteria*[4].

Rather than simply occupying space in our bodies, the intestinal microbiota is essential to nutrient metabolism, opportunistic pathogens defense[5], immune system development, and intestinal-barrier function regulation[3,6,7]. The specific balance of intestinal microbial diversity differs by individual according to variations (such as sanitation, social behaviors, and genetics)[8,9]. The beneficial balance of the intestinal microbial ecosystem can be disrupted by a series of factors, which includes antimicrobial drugs, vaccination, and dietary shifts[3]. Previous studies have suggested that intestinal microbiota alterations have been implicated in many gastrointestinal diseases and even systemic illnesses, such as metabolic diseases[10,11], neuropsychiatric conditions[12], autoimmune diseases[13], allergic disorders[14], and tumors[15].

Fecal microbiota transplantation (FMT) is a technique in which intestinal microbiota are transferred from a healthy donor to the patient, with the goal being to introduce or restore a stable microbial community in the gut. The first use of feces in such a manner was described, according to the Handbook of Emergency Medicine, approximately 1700 years ago by a Chinese medical scientist named Ge Hong[16]. It was first published in the English language by Eiseman *et al*[17] in 1958, when he reported a prompt response in patients with antibiotic-associated diarrhea treated with fecal enemas. Nevertheless, this practice was not well recognized until 1978, when investigators recognized *Clostridium difficile* infection (CDI) was the etiology of antibiotic-associated pseudomembranous colitis[18,19]. In the past few decades, the use of FMT for managing the increasing burdens of CDI has demonstrated it to be an effective therapeutic strategy for CDI[20-23]. In 2012, Borody *et al*[24] reported that more than 1200 cases have been treated in several centers. A total of 583 CDI patients treated with FMT produced a cumulative cure rate of more than 90% in 36 publications[25]. In addition, standardized frozen donor fecal bacterial preparations used in the treatment of recurrent CDI showed equal cure rates to fresh fecal samples[26]. 2013 guidelines for CDI have recommended that FMT should be considered if there is a third recurrence after a pulsed vancomycin regimen[27].

Although there are still many areas of uncertainty concerning this emerging technology, including transmission of infectious organisms, long-term sequelae, and even cost-effective evaluation, the United States Food and Drugs Administration have recently paid critical attention to FMT protocol in clinical applications. Borody *et al*[24] regarded the flora in feces as a special organ, and therefore considered the technique of FMT as a particular type of organ transplantation, regardless of the issue of immunological rejection. FMT has hence emerged as an important therapeutic modality in the manipulation of altered intestinal microbiota, with the indications of FMT possibly being expanded to even extra-intestinal conditions.

RATIONALE FOR FMT

The exact mechanisms by which intestinal dysbiosis becomes involved in disease development are not completely elucidated. Alteration of metabolic activities induced by perturbed intestinal bacterial species leads to weakened defense of the gastrointestinal mucosa, which in turn leads to increasing intestinal permeability and toxic substances being absorbed into the systemic circulation. Prior work has observed disruption of the intestinal microbiota being evident at the phylum level, with marked depletion in levels of probiotics and a relative increase in the numbers of pathogens leading to complications in intestinal conditions[27]. The alteration of microbial communities in both inflammatory bowel disease (IBD) and CDI patients was characterized by a reduction in two phyla of bacteria, *Firmicutes* and *Bacteroidetes*, which are prominent in healthy controls[28,29]. Moreover, an increase in *Proteobacteria* such as *Enterobacteriaceae* is also found in individuals with IBD[30]. *Bacteroides fragilis,* the prominent human gut commensal, can prevent and cure inflammatory disease *via* the effect of its symbiosis factor (polysaccharide A, an immunomodulatory bacterial molecule) on the activation of the Toll-like receptor 2 pathway, inducing regulatory T cells and interleukin-10 production[31]. Dextran sodium sulfate-induced colitis in a mouse model demonstrated that spore-forming *Firmicutes* in clostridial clusters IV and XIVa reduced intestinal inflammation through regulatory T cells induction[32].

These studies highlight the role of microbiota-target therapy for reinstalling the depleted bacterial species associated with the disease. Probiotics somehow alter

the metabolism of the indigenous gut flora, although the effect is largely restricted to limited bacterial species, and have a transient inhabitation effect on the intestine. Nevertheless, the satisfactory outcome of treatment with FMT suggests that feces contain a superior combination of intestinal bacterial strains and is more favorable for repairing disrupted native microbiota by introducing a complete, stable community of intestinal micro-organisms. Feces also harbors additional substances (proteins, bile acids, and vitamins) which might contribute to the recovery of gut function[20].

This scenario has in fact been documented in a recent study of FMT in recurrent CDI trying to elucidate the mechanism of action of fecal infusion[33]. The authors assessed the characteristics of fecal microbiota before, after, and during follow-up of FMT and found the intestinal microbiota changed persistently over time, from a less-diverse disease state (pre-FMT) to a more diverse ecosystem virtually resembling that of fecal donors (post-FMT). Such dynamic monitoring of the intestinal microbiota helps us to identify the key groups representing the ecosystem, as well as further illustrating that normalization of the bowel function was accompanied by the engraftment of intestinal micro-organisms from a healthy donor. Currently, there is significant interest in the area of FMT in IBD[34], especially with the evidence of an impressive curable effect in some ulcerative colitis (UC) patients[35,36]. A study was conducted to determine microbiota composition after FMT in 5 patients with UC by monitoring their fecal bacterial communities at multiple time points[37]. The results showed that one patient had a positive response to FMT, which was characterized by the augmentation of donor-derived microbiota, including *Faecalibacterium prausnitzii*, *Rosebura faecis*, and *Bacteroides ovatus*. According to Borody *et al*[38] Crohn's disease (CD) is less responsive to FMT when compared with UC. Nonetheless, recent case reports have shown the promising future of FMT as a rescue therapy for CD[39-41]. Data on the application of FMT in irritable bowel syndrome (IBS) is limited to a case series of 55 patients which showed that 36% of patients were regarded as curable while 16% had symptoms reduced[42,43]. To better understand the role of the intestinal microbiota in the etiology and effective treatment of IBD and IBS, future controlled trials are necessary.

For this reason, the core mechanism for the efficacy of FMT is likely to be the establishment of intestinal bacterial strains and antimicrobial components (adhesin, immunomodulatory molecules, bacteriocin, *etc.*) produced by these associated strains. Adhesin molecules can compete for sites with pathogens, leading to them being prevented from colonizing in the intestine and rehabilitating the intestinal microbiota[5].

SAFETY OF FMT

When FMT entered the medical community, it became a relatively hot therapeutic strategy, bringing with it both promise and controversy. According to published articles, transient adverse responses after FMT have been reported, including mild fever, abdominal pain, diarrhea, exhaust, flatulence, and fatigue[36]. However, these adverse effects are self-limiting. De Leon *et al*[22] reported a UC patient quiescent for more than 20 years who developed a flare of UC after FMT. This case gives us cautionary information concerning FMT being used to treat CDI with UC. Moreover, a recent paper reported a UC patient who had a cytomegalovirus infection after performing home FMT without donor screening[44]. As extracts of feces are mediators between the donor and recipient, FMT has the potential for transmitting occult infections even when strict donor screening is performed.

FMT FOR EXTRA-INTESTINAL DISORDERS

It seems to be serendipitous that the CDI epidemic facilitated the application of FMT to many other diseases (Table 1). The pathogenesis of gut microbiota in extra-intestinal diseases was inspired by massive studies in germ-free (GF) animals. Complete construction of the hypothalamic-pituitary-adrenal axis requires the participation of gut microbiota[45]. GF mice exhibit a dysregulation of the axis, thereby resulting in altered brain-derived hormones (*e.g.*, norepinephrine and tryptophan) and increased caloric intake[45]. Aside from the crucial role of intestinal microbiota in central nervous system activity, another concept is emerging which was termed as "bidirectional brain-gut-microbiota axis"[46-48]. The destruction of the axis leads to altered behaviors and various neurologic conditions[49,50]. Identically, ample human studies have provided evidence for the critical role of the gut microbiota in extra-intestinal disorders.

Metabolic diseases

There is compelling evidence that the intestinal microbiota is closely linked to a series of metabolic conditions. Obesity, diabetes mellitus, and metabolic syndrome are epidemic in modern society. There have been extensive investigations concerning microbiota reaction acting as a pivotal role in the pathogenesis of these endocrine diseases in animal models[51,52]. Changes in gut microbiota composition have also been reported in obese humans[53-55], with a shift in the ratio of *Firmicutes* and *Bacteroidetes*[56]. Meanwhile, increased levels of bacteria and their metabolic products were found in the plasma of obese individuals, with one likely mechanism thought to be increased intestinal permeability[57,58]. Recent studies have shown that short chain fatty acid (including butyrate) producing *Clostridiales* strains (*Roseburia* and *Faecalibacterium prausnitzii*) were found to be decreased in patients with type 2 diabetes mellitus, but non-butyrate producing *Clostridiales* and pathogens such as *Clostridium clostridioforme* were increased[59,60]. Vrieze *et al*[61] conducted

Table 1 Summary of extra-intestinal disorders associated with gut microbiota

Extra-intestinal disorders	Ref.	Publication year	Study type
Metabolic diseases			
Metabolic syndrome	Vrieze *et al*[61]	2012	RCT[1]
Obesity	Turnbaugh *et al*[54]	2009	Observational study
	Armougom *et al*[56]	2009	Observational study
	Schwiertz *et al*[55]	2010	Observational study
	Greenblum *et al*[53]	2012	Observational study
	Parks *et al*[52]	2013	Experimental study
Type 2 diabetes mellitus	Qin *et al*[59]	2012	Observational study
Cardiovascular diseases	Wang *et al*[62]	2011	Experimental study
	Tang *et al*[65]	2013	Experimental study
	Koeth *et al*[66]	2013	Experimental study
Non-alcoholic fatty liver	Rabot *et al*[73]	2010	Experimental study
	Le Roy *et al*[68]	2013	Experimental study[1]
Neuropsychiatric disorders			
Parkinson's disease	Ananthaswamy[74]	2011	Case report[1]
Multiple sclerosis	Borody *et al*[76]	2011	Case report[1]
Myoclonus dystonia	Borody *et al*[78]	2011	Case report[1]
Autism	Finegold *et al*[79]	2002	Observational study
	Song *et al*[82]	2004	Observational study
Chronic fatigue syndrome	Borody *et al*[84]	2012	Cohort study[1]
	Frémont *et al*[83]	2013	Observational study
Autoimmune disorders			
ITP	Borody *et al*[85]	2011	Case report[1]
Arthritis	Scher *et al*[88]	2013	Observational study
	Abdollahi-Roodsaz *et al*[86]	2014	Experimental study
SS and SLE	Szymula *et al*[91]	2014	Experimental study
Hashimoto's thyroiditis	Corapçioğlu *et al*[93]	2002	Observational study
	Strieder *et al*[92]	2003	Observational study
	Sasso *et al*[96]	2004	Observational study
	Effraimidis *et al*[95]	2011	Observational study
Allergic disorders			
Atopy	Dotterud *et al*[107]	2010	RCT
	Herbst *et al*[101]	2011	Experimental study
	Schabussova *et al*[105]	2012	Experimental study
Asthma	Jang *et al*[104]	2012	Experimental study
	Stensballe *et al*[102]	2013	Observational study
Extra-intestinal tumors	Gold *et al*[15]	2004	Observational study
Mammary tumors	Rao *et al*[111]	2006	Experimental study
	Rao *et al*[112]	2006	Experimental study
Hepatocellular carcinoma	Fox *et al*[114]	2010	Experimental study
Lymphoma	Yamamoto *et al*[115]	2013	Experimental study

[1]Fecal microbiota transplantation used in these studies. RCT: Randomized controlled trial; ITP: Idiopathic thrombocytopenic purpura; SS: Sjögren's syndrome; SLE: Systemic lupus erythematosus.

a double blind, randomized controlled trial of FMT in 18 male patients with metabolic syndrome. Half of them received fecal microbiota infusion from lean male donors (allogenic group), while the other half received auto-fecal transplants (control group). The results showed that both insulin sensitivity and levels of butyrate-producing intestinal microbiota (*Roseburia intestinalis* and *Eubacterium hallii*) were markedly increased after a six-week infusion of microbiota from lean donors, while no significant changes were found in the control group[61]. In the group following allogenic gut microbiota transfer, the median rate of glucose disappearance increased from 26.2 to 45.3 μmol/kg per minute, while the median endogenous glucose production increased from 51.5% to 61.6%. Hence, it can be speculated that FMT could be developed as a potential therapeutic strategy for increasing insulin sensitivity in humans.

Leaky gut or loss of intestinal integrity may facilitate the development of cardiometabolic disorders due to alterations in composition and diversity of gut microbiota. A close association of microbial translocation with the risk of cardiovascular disease (CVD) have recently been established[62,63], with probiotic bacteria having raised plasma unconjugated bile acid concentrations through modulation of the enterohepatic circulation[64]. It also concomitantly reduced the lipid uptake from the intestine and the plasma cholesterol level, an indirect risk marker of CVD, by means of regulation of a series of signaling molecules, such as Farnesoid X receptor-α and G-protein-coupled receptors[64]. One study illustrated the negative impact of trimethylamine-*N*-oxide, an atherogenic compound produced by intestinal flora from choline and betaine[65,66], on the morbidity and mortality of cardiovascular events[67]. A variety of data have clearly

demonstrated that the intestinal microbiota act as an independent risk factor for CVD, as well as representing a promising therapeutic target for this disease.

An increasing body of published evidence has recently been generated that demonstrates that demonstrates the gut microbiota act as an epigenetic factor driving the progression of non-alcoholic fatty liver disease (NAFLD)[68-70], a metabolic syndrome that manifests in the liver[71]. Intestinal dysbiosis promotes hepatic injury and inflammation through either a breakdown of the intestinal barrier or translocation of microbial products[72]. Abundant studies using GF mice models have illustrated that these special organisms are resistant to steatosis and diet-induced obesity[73]. Le Roy *et al*[68] performed an animal study to clarify the role of gut microbiota in the development of NAFLD. They divided the conventional mice into two groups (responder and non-responder) according to their response to a high-fat diet (HFD), and found that GF mice receiving FMT from different donors (responder and non-responder) developed comparable results on the HFD. The GF group that received microbiota from the responder group developed steatosis and harbored a larger number of *Barnesiella* and *Roseburia*, whereas *Allobaculum* was higher in the other group[68]. Further evidence has proved that intestinal permeability increased and endotoxemia developed in NAFLD patients. This indicates that microbiota-targeting therapy might be useful in treating NAFLD and obesity.

Neuropsychiatric disorders

A high incidence rate of constipation is found in Parkinson's disease (PD) patients. Constipation can precede the onset of motor symptoms by more than 10 years[50], indicating the disease may start in the intestine. A man suffered from PD and characterized with the motor symptoms of marked pill-rolling hand tremors, micrographia, cogwheel rigidity, and chronic constipation[74]. He received antibiotic therapy (vancomycin, colchicine, and metronidazole) for his constipation and reported an improvement in gastro-intestinal symptoms. After consistent therapy for 10 mo, his neurologic symptoms disappeared. This case cured by antibiotics suggests that the gut microbiota are involved in the pathogenesis of PD[74]. The results of symptomatic improvement in PD patients by FMT indicate a new way of thinking for clinicians[75].

Both animal and clinical studies have shown that the pathogenesis of multiple sclerosis (MS) is associated with the intestinal microbiota[76,77]. Three patients with MS who underwent FMT for constipation achieved normal defecation and virtually complete normalization of neurological symptoms, thereby improving their quality of life[76]. Borody *et al*[78] reported a case of a young female patient with myoclonic dystonia and chronic diarrhea. The symptoms had co-developed since she was 6 years old and progressed in severity to a plateau. FMT resulted in a rapid improvement in diarrhea symptoms, a 90% improvement in her myoclonus dystonia symptoms, and, as a consequence of restoring her fine motor function, improving her ability to perform tasks that require dexterity, such as holding cups and fastening buttons[78].

Autism is another condition in which intestinal microbiota is implicated. The onset of autism is often accompanied by intestinal dysfunction[79-81]. The first description of an association between autism and gastrointestinal syndrome began in 1971, with a report that 6 out of 15 autism patients had changed fecal character and defecation frequency[81]. Finegold *et al*[79] performed an intestinal flora study in regressive autism. It is compelling to observe that there were higher counts of *Clostridium* and *Ruminococcus spp.* in the stools of autistic children when compared to those in the control group. Nine clostridial species were found in autistic children, while only three were found in healthy children. The authors further observed histologic changes in the gastric and duodenal specimens. Moreover, significant higher numbers of non-spore- forming anaerobes and microaerophilic bacteria were found in autistic children. Based on the hypothesis that autism involves intestinal microbiota, Song *et al*[82] characterized *Clostridia* from the feces of autistic and control children. The data indicate that counts of *Clostridium bolteae* and clusters I and XI in autistic group are largely greater than those in control children. There was evidence of autistic symptom remission in two children after FMT[49]. Parallel results were also presented in five children who received daily cultured *Bacteroidetes* and *Clostridia* for several weeks.

Alterations in the intestinal flora have also been observed in patients with chronic fatigue syndrome (CFS)[83]. The proportion of gram-negative *Escherichia coli* was reduced in CFS patients versus that in healthy controls (49% *vs* 92.3%). More recent research examined a larger cohort of 60 CFS patients with gastrointestinal symptoms who had underwent FMT[84]. The results showed that 42/60 (70%) patients responded to treatment and 7/12 (58%) retained complete resolution of symptoms during a 15-20 year follow-up period. These results, suggest that FMT may play a role in the treatment of CFS.

Autoimmune diseases

The incidence of autoimmune diseases has dramatically increased, but the causes of these conditions remain poorly understood. Idiopathic thrombocytopenic purpura (ITP) is caused by the production of autoantibodies against platelet surface antigens. In a patient with ITP who was treated with FMT for UC, prolonged reversal of ITP was reported and the normalization of platelet levels was achieved[85].

The onset of rheumatoid arthritis (RA) is multifactorial and requires both genetic and environmental influential factors, with the commensal intestinal microbiota playing a major role[13,86,87]. Alterations in the intestinal microbiome can have an extended effect on RA through mucosal immune activation. Previous reports have implicated *Prevotella copri* in the pathogenesis of RA[88]. A recent study

used the interleukin-1 receptor antagonist deficient (IL-1Ra$^{-/-}$) mouse model, which can spontaneously develop T cell-driven IL-17-dependent autoimmune arthritis[86]. It was shown that IL-1Ra$^{-/-}$ mice had increased Th17 and a reduced proportion of Th1 in small intestinal lamina propria compared with wild-type mice. GF IL-1Ra$^{-/-}$ mice had lower levels of both Th1 and Th17. Interestingly, IL-1Ra$^{-/-}$ mice previously treated by antibiotics was recolonized by segmented filamentous bacteria, a prominent Th17 inducer, leading to full-fledged arthritis. Moreover, elimination of intestinal Gram-negative commensals suppressed the progression of arthritis[86]. Understanding the role of the intestinal microbiota in the onset of RA may provide significant attention to FMT with regards to management of the disease; the potential is therefore worthy of consideration.

In both Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE), Sjögren's syndrome antigen A/Ro60 is one of the main autoantigens. Ro60 reactive autoantibodies are associated with manifestation severity in SS[89] and with photosensitivity in SLE[90]. *Escherichia coli* expresses von Willebrand factor type A domain protein, which can activate Ro60-reactive T cells[91]. Therefore, immune responses to the gut microbiota may play a pivotal role in the initiation of autoimmunity in SLE and SS. This sheds a light on a novel therapeutic strategy for the diseases.

Hashimoto's thyroiditis (HT) is a thyroid autoimmune disorder, and a series of studies have been implemented to explore the link between gut micro-organisms and HT[92-95]. Although no data on gut microbiota composition are available in HT, increased intestinal permeability was detected in patients with HT[96]. The onset of HT is associated with *Yersinia enterocolitica,* though conflicting data has also been presented[92,95]. Further work is required to test the hypothesis that the gut microbiota is an epigenetic factor for triggering HT, and thereby determine whether FMT is favorable for managing the illness.

Allergic disorders

The prevalence of allergic diseases has been increasing in modern society over the past 50 years. To date, there are two hypotheses for the allergy pandemic[97]: the hygiene hypothesis[98] and the microbiota hypothesis[99]. The latter hypothesis suggests that the disruption of intestinal microbiota drives the emergence of allergy. A wealth of studies regarding the relationship between allergic diseases and microbiota has been conducted in both humans and mice. In the model of allergic airway inflammation induced by ovalbumin/alum, GF mice develop more severe allergic disease than conventional mice[100,101]. Moreover, accumulating evidence has suggested early-life antibiotic exposure is involved in the development of atopy, such as allergic asthma and food allergies, with an altered composition of intestinal microbiota possibly being involved[102,103]. Though probiotic strategies have shown some promise in animal models in preventing asthma development[104,105], it has had little success in humans[106,107]. The use of FMT seems promising in restoring immune homeostasis by transferring a complex community of bacteria which is more stable and harbors a greater ability to colonize[97].

POTENTIAL THERAPEUTIC ROLE IN EXTRA-INTESTINAL TUMORS

A strong association has now been illustrated between the intestinal microbiota (*e.g., Streptococcus bovis, Enterococcus spp,* enterotoxigenic *Bacteroides fragilis*, pathogenic *Escherichia coli*, and *Fusobacterium nucleatum*) and colorectal cancer[108-110]. Recently, incremental data has suggested that the gut flora (namely *Streptococcus bovis* and *Helicobacter hepaticus*) might be involved in extra-intestinal tumors. Gold *et al*[15] reviewed 8 extraintestinal malignancies [3 pancreatic adenocarcinomas, 1 lung cancer, 1 ovarian cancer, 1 endometrial cancer, 2 non-solid-organ malignancies (1 chronic myelogenous leukemia with blast crisis and 1 chronic lymphocytic leukemia with end-stage liver disease)] in 45 cases with *Streptococcus bovis* bacteremia in a retrospective study, which suggested that extraintestinal malignancy might be warranted in patients with *Streptococcus bovis*. In addition, prior work has shown the gut microbiota is also involved in mammary tumors[111,112]. The authors infected recombination-activating gene 2-deficient multiple intestinal neoplasia ($Apc^{Min/+}$) mice with *Helicobacter hepaticus* and found the gut flora modulated the carcinogenesis of both mammary carcinoma and intestinal adenocarcinoma in females by triggering inflammatory responses. On a similar note, Rao *et al*[113] emphasized the question as to whether the gut bacteria should be examined in terms of prevention and treatment for mammary cancer.

In addition, Fox *et al*[114] used a mouse model to examine the hypothesis that specific intestinal bacteria were associated with hepatocarcinogenesis. The progress of hepatocellular carcinoma induced by aflatoxin and hepatitis C transgene was promoted by *Helicobacter hepaticus* colonization in the intestine through activation of the nuclear factor-κB pathway, which was associated with immunity in the intestine and liver. Surprisingly, neither hepatitis nor bacterial translocation to the liver was essential during this course. These results lead us to think of intestinal bacteria as an attractive therapeutic target.

More recently, Yamamoto *et al*[115] investigated the relationship between the gut microbiota and lymphoma. Using an *Atm*$^{-/-}$ mouse model (mice with ataxia-telangiectasia, which can eventually developed into lymphoma), the authors compared the incidence of lymphoma in isogenic mice reared in 2 distinct housing conditions, and found that the gut microbiota acted as a potential contributor to lymphoma onset. Meanwhile, *Lactobacillus johnsonii* was identified to be abundant in more cancer-resistant mice and was further tested for its ability to confer reduced systemic inflammation and

genotoxicity when re-established by oral transfer. Given that gut microbiota impact lymphoma incidence and latency, FMT holds promise for reducing lymphoma risk in susceptible individuals.

CONCLUSION

FMT is proven to be a well-established procedure and the most effective therapy for recurrent CDI to date. Case studies suggest that FMT also has potential clinical applications in treating a wide spectrum of other conditions associated with intestinal dysbiosis. However, additional high quality data are urgently needed to further establish the efficacy of FMT. It is expected that the standardization of FMT will be established in the coming years and its indications expanded. For this reason, besides conventional approaches, FMT is promising as an alternative therapy for many extra-intestinal disorders associated with gut microbiota.

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