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Review Article

Gut Dysbiosis and Fecal Microbiota Transplantation in Pancreatic Cancer: Current Status and Perspectives

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with difficulties in early diagnosis, poor prognosis, and limited effective therapies. Early detection and effective treatment offer the optimal chance to improve survival rates. Various studies have shown that gut microbiota dysbiosis is closely related to PDAC, with potential mechanism involving immune regulation, metabolic process impact, and reshaping the tumor microenvironment. A comprehensive understanding of the microbiota in PDAC might lead to the establishment of screening or early-stage diagnosis methods, implementation of cancer bacteriotherapy such as fecal microbiota transplantation, creating new opportunities and fostering hope for desperate PDAC patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal human malignancies. Through extensive efforts and prolonged research, the five-year survival rate has improved to approximately 10%.[1] Surgical resection offers a potential cure for patients with PDAC.[2] Due to the insidious onset and lack of specific early clinical manifestations, only 15–20% of patients are diagnosed with PDAC that can be removed using standard resection.[3] It is urgent to find effective biomarkers and clinical treatment strategies.

The gut microbiota, consisting of trillions of microorganisms inhabiting the intestinal tract, interacts with the host in various ways, playing crucial roles in host physiology, including immune regulation, metabolite exchange, and nutrient metabolism.[4,5] With the progress of metagenomics and the identification of gut bacterial compositions, studies on the role of gut microbiota in cancer have become an international hotspot. Growing research suggests a strong link between the gut microbiome and PDAC, indicating a critical role in the development, progression, and treatment of the disease.[6] Therefore, utilizing microbiota therapy to reconstruct the composition and quantity of the gut microbiome may be a potential therapeutic strategy for PDAC.[7,8]

Among all the approaches for interventions targeting the gut microbiome, fecal microbiota transplantation (FMT), which involves transferring functional microbiota from healthy donors into the gastrointestinal tract of patients, has shown initial clinical effects in cancer therapy.[9] Numerous clinical studies have demonstrated that FMT can significantly enhance the efficacy of tumor immunotherapy, chemotherapy, and radiotherapy, and mitigate adverse effects.[10] Nevertheless, concerns persist regarding the safety, efficacy, and precision of FMT procedures.

Herein, we provide an overview of the complex association between gut microbiota and PDAC, as well as the current research progress and prospects of FMT in the management of PDAC, with at least one published or ongoing FMT study in human or mouse models. Furthermore, we discuss recent challenges and offer future research directions.

The human gut microbiome

Under healthy conditions, the gut microbiota is stable, resilient, and maintains a mutually beneficial relationship with the host.[11,12] The composition of the gut microbiota is influenced by various factors, including diet, physical activity, daily routines, host age, gender, genetics, and the use of antibiotics, probiotics, and other microbiome-targeted interventions.[13] Consequently, defining the precise characteristics of a healthy gut microbiota is challenging. Generally, the human gut microbiota is dominated by five bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia.[13] Elderly individuals often show reduced levels of Bifidobacterium and elevated levels of Clostridium and Proteobacteria.[14] Additionally, based on the composition of the gut microbiota, individuals can be classified into three enterotypes,

Keywords: Fecal microbiota transplantation; Pancreatic cancer; Oncogenesis; Gut microbiota; Microbiota-derived metabolites; Cancer therapy; Biomarker.

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which are not influenced by gender, age, nationality, or geographical location. Enterotype 1 is characterized by Bacteroides as the indicative taxon; Enterotype 2 is driven by Prevotella; and Enterotype 3 is distinguished by the relative abundance of Firmicutes, primarily Ruminococcus.[15]

Gut dysbiosis in PDAC

Gut microbiome in PDAC

Dysbiosis of gut bacteria is a well-established phenomenon that contributes to several aspects of PDAC.[16] In recent years, multiple studies have analyzed the gut microbiota in stool samples obtained from PDAC patients and non-tumor controls through 16S ribosomal RNA sequencing and metagenomic sequencing, revealing notable differences in gut microbiota composition. Nagata and colleagues analyzed the gut microbiota of PDAC patients and controls from Japanese, Spanish, and German cohorts, finding a significant enrichment of Streptococcus and Veillonella spp., along with a reduced abundance of Faecalibacterium prausnitzii, as characteristic gut signatures associated with PDAC across all three cohorts.[17] A study conducted by Zhou and colleagues,[18] which included PDAC patients (32), autoimmune pancreatitis patients (32), and healthy controls (32), showed a marked increase in the phylum Proteobacteria and a decrease in the phylum Firmicutes in PDAC patients compared to autoimmune pancreatitis patients and controls. Additionally, meta-analyses and prospective cohort studies have suggested a positive correlation between Helicobacter pylori infection and PDAC, indicating that patients with Helicobacter pylori infection have a higher risk of developing PDAC.[19,20] The characteristics of gut microbiota in PDAC patients vary across different studies, which may be due to substantial geographical and ethnicity-specific heterogeneity of the gut microbiota, differences in fecal collection, and sequencing protocols. Therefore, larger-scale investigations are warranted to develop a comprehensive gut microbiota profile unique to PDAC.

The characteristic alterations observed in the gut microbiota of PDAC patients are being proposed as promising biomarkers for the diagnosis of PDAC. Kartal *et al*.[21] assessed the gut microbiota of 57 PDAC patients, 50 controls, and 29 chronic pancreatitis patients to construct fecal metagenomic classifiers based on 27 microbial species, achieving an accuracy of up to 0.84 in the area under the receiver operating characteristic curve (AUC), which accurately identified PDAC. Furthermore, when combined with CA199, the AUC increased to 0.94, demonstrating high predictive accuracy in 26 validation cohorts.[21] Similarly, Yang and colleagues, comparing the gut microbiota of 44 PDAC patients and 50 healthy individuals, identified Streptococcus as an accurate discriminator of PDAC (AUC = 0.927) and PDAC with liver metastasis (AUC = 0.796), suggesting its utility as an effective screening tool.[22] Considering the convenience and non-invasiveness of gut microbiota detection, along with high compliance in the initial screening population, gut microbiota-related markers hold promise as valuable tools for PDAC screening and early diagnosis.

Gut dysbiosis and immune regulation

The complex interplay between the gut microbiota and the immune system regulates host immunity via various pathways, leading to either immune activation or suppression, consequently impacting the onset and treatment of PDAC.[16,23] KRAS mutation is one of the initiating factors in PDAC.[24] Lipopolysaccharides, the major components of gram-negative bacterial cell walls, can activate Toll-like receptor signaling pathways and stimulate the secretion of cytokines such as IL-8 and TNF-α.[25] In mouse models of PDAC, gut microbiome depletion significantly reduced tumor volumes and the number of both primary and liver metastatic tumors, with an increase in interferon gamma-producing T cells and a corresponding decrease in interleukin 17A and interleukin 10-producing T cells in the tumor microenvironment.[26] Moreover, gut microbiota may migrate into the pancreas, exerting immunosuppressive effects. Pushalkar and colleagues found that intrapancreatic bacteria were elevated in PDAC compared with normal pancreatic tissue, and certain bacteria were selectively increased in PDAC compared with the gut.[27] Furthermore, bacterial ablation was shown to inhibit PDAC growth and was associated with immunogenic reprogramming of the tumor microenvironment, including a reduction in the activation of specific Toll-like receptors on monocytic cells and an increase in the polarization of tumor-protective M1 macrophages, which facilitated the infiltration and activation of T helper cells and cytotoxic T cells.[27] Alam *et al*.[28] discovered that the intratumoral fungal mycobiome drives IL-33 secretion, promoting type 2 immune responses and accelerating PDAC progression.

Microbiota-derived metabolites and their effects on PDAC

Metabolites produced by the gut microbiota play crucial roles in various physiological and pathological processes, including cell proliferation, differentiation, apoptosis, and even tumor treatment.[6] Short-chain fatty acids, primarily including acetate, propionate, and butyrate, are the most abundant microbial metabolites in the colonic lumen and are mainly produced by the microbial fermentation of prebiotics. Among short-chain fatty acids, butyric acid has been shown to activate differentiation and inhibit invasion in PDAC cells.[29–31] In PDAC patients, lower concentrations of butyrate and reduced relative abundance of butyrate-producing bacteria in the gut have been reported. More recently, indole-3-acetic acid, a tryptophan metabolite produced by Bacteroides fragilis and Bacteroides thetaiotaomicron, enhanced the efficacy of chemotherapy in PDAC. In combination with chemotherapy, it downregulates the reactive oxygen species-degrading enzymes glutathione peroxidase 3 and glutathione peroxidase 7, leading to the accumulation of reactive oxygen species and downregulation of autophagy in PDAC cells, thereby inhibiting cell proliferation.[32] Mirji *et al*.[33] identified that the gut microbe-derived metabolite trimethylamine N-oxide enhanced immunotherapy sensitivity, associated with an immunostimulatory tumor-associated macrophage and activated effector T cell response in the tumor microenvironment. Uro A, an intestinal microbial metabolite of ellagitannin, inhibited phosphorylation of AKT and p70S6K through the PI3K/AKT/mTOR pathway and induced strong antiproliferative and proapoptotic effects in PDAC, along with reduced levels of infiltrating immunosuppressive cell populations such as myeloid-derived suppressor cells, tumor-associated macrophages, and regulatory T cells.[34] Altogether, the biological activity of microbiota-derived metabolites in PDAC still needs to be further explored.

Gut dysbiosis and PDAC treatment

Systemic therapy, which includes chemotherapy as the primary treatment modality supplemented by radiotherapy, targeted therapy, immunotherapy, and other approaches, remains crucial in managing PDAC.[35] The gut microbiome has been shown to influence the efficacy of these treatments. For instance, gemcitabine, a commonly used chemotherapy drug for PDAC, may have reduced efficacy due to Gammaproteobacteria, which are suggested to migrate from the gut to pancreatic tumors.[36] FOLFIRINOX, consid-

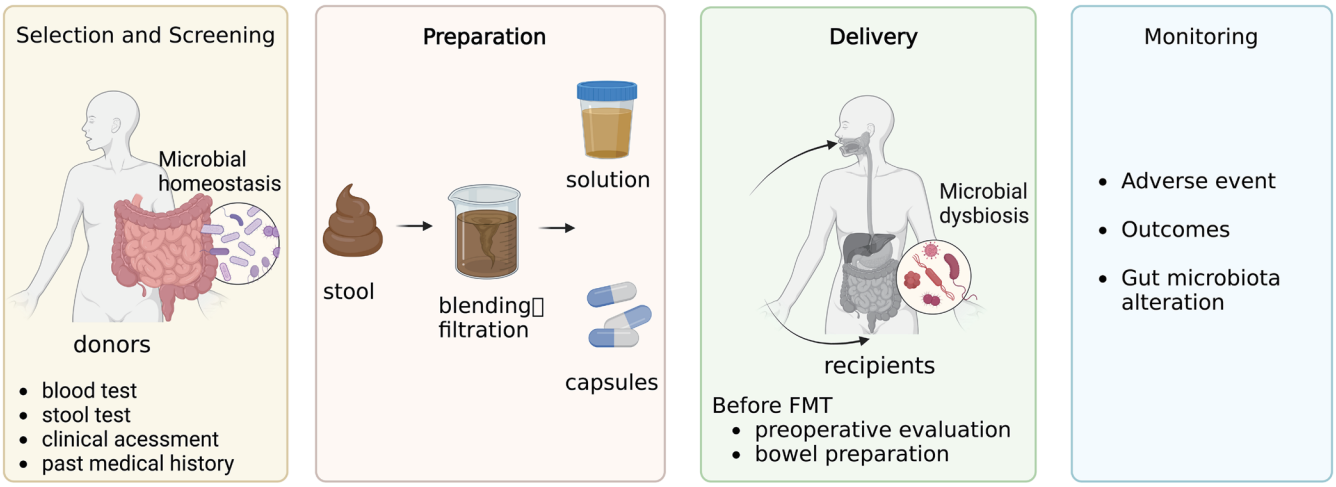

Fig. 1. The process of FMT (fecal microbiota transplantation). This includes (1) selection and screening for donors; (2) bacterial suspension and freeze-dried capsules preparation; (3) delivery via upper gastrointestinal routes (nasogastric tube, gastroscopy) or lower gastrointestinal routes (colonoscopy, sigmoidoscopy); (4) close post-transplant follow-up.

ered frontline therapy for advanced PDAC, consists of leucovorin, fluorouracil, irinotecan, and oxaliplatin. Irinotecan is metabolized in the liver to SN-38G, an inactive metabolite. However, in the intestines, bacterial β-glucuronidase enzymes produced by the commensal microbiota can convert SN-38G back into its active form, SN-38.[37,38] This activation process in the intestines can lead to delayed diarrhea.[39] Antibiotics have the potential to disrupt the gut microbiota's composition. A study involving 20 volunteers exposed to four common antibiotic regimens showed a significant decrease in species richness immediately after treatment. While most volunteers' microbiomes returned to pre-treatment richness after two months, the taxonomy and metabolism were altered.[40] However, some volunteers experienced a persistent reduction in microbiome diversity.[40] For tumor patients treated with immunotherapy, antibiotic administration is associated with poor progression-free survival and overall survival. Therefore, caution should be exercised when prescribing antibiotics to patients planning to undergo immunotherapy.[41–43] Park *et al*.[44] identified that the gut microbiota can promote responses to programmed death 1 (PD-1) checkpoint blockade by downregulating the programmed death-ligand 2-glycosylphosphatidylinositol-anchored membrane protein b (PD-L2-RGMb) pathway in FMT. Interestingly, the gut microbiome could be linked to postoperative complications after pancreatic surgery. In a prospective clinical pilot study, Schmitt *et al*.[45] analyzed 116 stool samples from 32 patients before and after pancreatic surgery and revealed that distinct microbiome patterns are associated with surgical complications. Patients with a specific gut microbial composition pattern, characterized by an increase in Akkermansia, Enterobacteriaceae, and Bacteroidales, and a decrease in Lachnospiraceae, Prevotella, and Bacteroides, were found to be at a significantly higher risk for developing postoperative complications.[45] Overall, the intricate relationship between the gut microbiome and treatment outcomes in PDAC underscores the importance of preserving microbiome integrity during therapy.

An overview of FMT

FMT is a therapeutic approach that delivers the full spectrum of gut microbiota to patients to combat or alleviate microbial imbalances. Historical records in traditional Chinese medicine document the use of feces to treat illnesses, dating back approximately 1,700 years when Ge Hong used human fecal infusions to treat patients on the brink of death due to food poisoning, diarrhea, and fever.[46] In modern medicine, FMT was first approved for the treatment of multiply recurrent or refractory Clostridioides difficile infection.[47] In 2023, the first international Rome consensus conference on gut microbiota and fecal microbiota transplantation in inflammatory bowel disease was published.[48] Currently, in clinical practice, FMT has been applied to treat various diseases associated with intestinal dysbiosis, including inflammatory bowel disease,[49] irritable bowel syndrome,[50] diarrhea,[51] as well as disorders of the nervous and metabolic systems,[52–54] and cancer,[51,55] with its effectiveness and safety widely recognized.

Based on consensus from various regions, the implementation of FMT can be broadly divided into several steps (Fig. 1): donor selection, preparation of transplant material, recipient preparation, transplantation, and post-transplant follow-up management.[56,57] (1) Prior to FMT implementation, rigorous donor screening and regular assessment of donor health status are necessary; (2) Recipients must undergo comprehensive clinical evaluation before transplantation and prepare their intestines according to their individual conditions; (3) Transplant materials are typically in the form of a solution or freeze-dried capsules derived from donor feces. The method of transplantation varies depending on the type of transplant material, with options including infusion of the solution via upper gastrointestinal routes (nasogastric tube, gastroscopy) or lower gastrointestinal routes (colonoscopy, sigmoidoscopy) to introduce functional microbial communities into the patient's intestines; (4) Close post-transplant follow-up is essential to monitor the therapeutic efficacy of FMT and any associated adverse reactions.

Potential mechanisms of FMT

FMT has gained attention for its potential to treat cancer by altering the composition of gut microbiota. While the precise mechanisms underlying FMT are still under investigation, several potential pathways have been proposed (Fig. 2). FMT can replenish

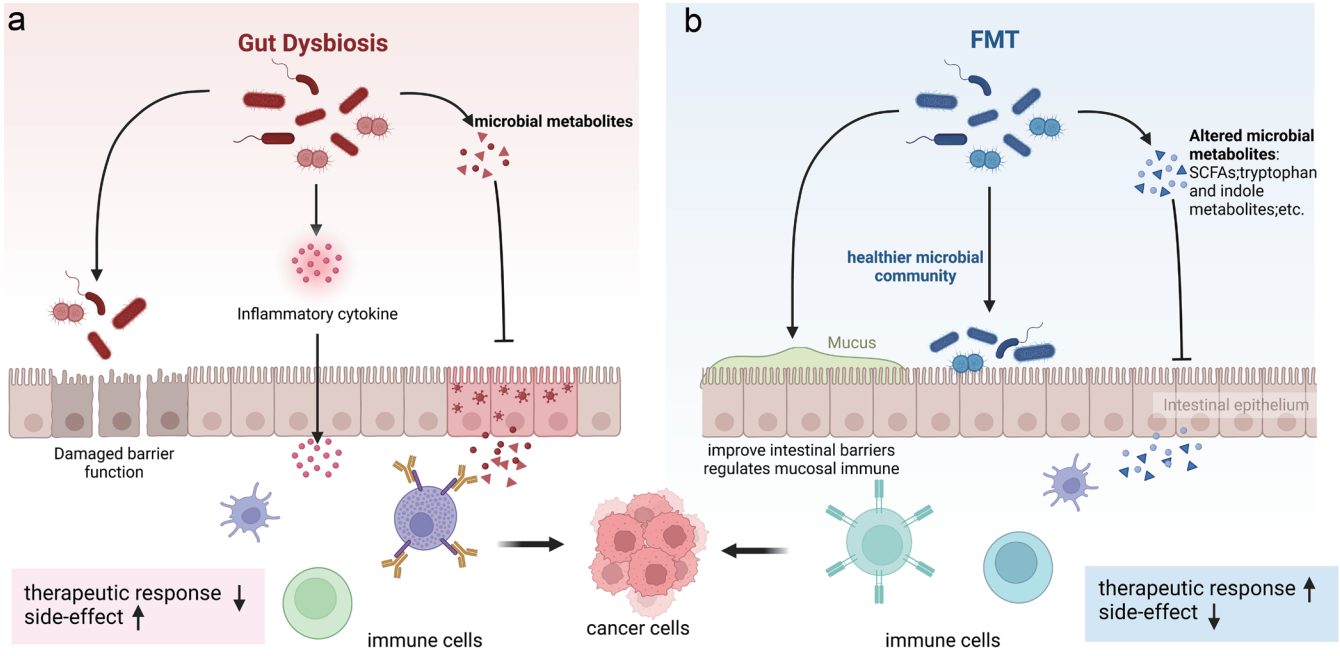

Fig. 2. Gut dysbiosis and fecal microbiota transplantation for cancer. (a) Potential mechanisms by which a disturbed gut microbiome contributes to cancer pathogenesis. (b) Proposed mechanisms by which FMT restores the gut microbiome and reestablishes microecosystem homeostasis. FMT, fecal microbiota transplantation; SCFA, short-chain fatty acids.

and diversify the recipient's gut microbiota, correcting imbalances and fostering a healthier microbial community, which improves intestinal barriers and regulates mucosal immunity. Huang *et al*.[58] discovered that FMT reduced gut inflammation by decreasing toll-like receptor 4. It also provided significant relief from intestinal mucosal injury and reduced intestinal permeability by increasing the expression of mucin and tight junction proteins.[58] The intestine, as the largest immune organ in the human body, plays a pivotal role in maintaining host balance and defense through its mucosal immune system. The intestinal microbiome promotes the differentiation of naive $CD8^+$ T cells into $CD4^+$ T cells in the large intestine.[59] FMT may also impact metabolites that regulate and alleviate tumors locally in the gut or systemically throughout the body. Inosine, a prominent microbial metabolite, in the presence of exogenous interferon-gamma, promotes T helper 1 cell differentiation by binding to the adenosine 2A receptor on the surface of T cells and significantly enhances the anticancer ability of T helper 1 cells in tumors.[60]

FMT and PDAC treatment

FMT is a potent approach to restoring gut microbiota, and several preclinical models have demonstrated its potential in treating PDAC. Pushalkar *et al*.[27] conducted mouse-to-mouse FMT experiments and observed that mice receiving fecal samples from PDAC mice exhibited accelerated tumor growth compared to those receiving samples from control mice. This suggests that FMT modulates tumor growth by altering the gut microbiota. Riquelme *et al*.[61] conducted FMT experiments in mice using samples from PDAC patients with short-term survival (STS), PDAC patients with long-term survival (LTS), and healthy controls. They found that mice receiving fecal samples from LTS patients exhibited significantly slower tumor growth compared to those transplanted with samples from STS patients ($P < 0.001$) or controls ($P = 0.02$). Moreover, there was a notable increase in the infiltration of $CD8^+$ T cells and activated T cells in the tumor microenvironment of mice that received FMT from LTS patients. Conversely, mice that received FMT from STS patients showed an increase in the infiltration of $CD4^+FOXP3^+$ cells and bone marrow-derived suppressor cells in the tumor. These findings indicate that FMT therapy can modulate the tumor immune microenvironment and the natural history of the disease.

FMT and chemotherapy

Chemotherapy is one of the primary methods for systemic treatment of PDAC; however, drug resistance limits its effectiveness and is a major cause of recurrence and poor prognosis in PDAC patients.[62,63] Recently, growing evidence suggests that microbes impact the efficacy of chemotherapeutic drugs in cancer therapies. Bacterial modification of pharmaceuticals might either potentiate desirable effects, compromise efficacy, or release harmful compounds, both directly and indirectly.[64] It is reported that bacteria can metabolize the chemotherapeutic drug gemcitabine (2′,2′-difluorodeoxycytidine) into its inactive form (2′,2′-difluorodeoxyuridine), which depends on the bacterial enzyme cytidine deaminase.[36] In a preclinical study, Tintelnot *et al*.[32] utilized patient-to-mouse FMT experiments and observed that mice receiving fecal samples from chemotherapy-responder patients exhibited increased sensitivity to chemotherapy compared to those receiving samples from chemotherapy-non-responder patients. Additionally, receiving fecal samples from healthy mice led to a reduction in tumor growth.[32] These studies lay the foundation for conducting clinical trials of FMT alongside chemotherapy for PDAC.

FMT and radiotherapy

Radiotherapy is an important modality for the local treatment of PDAC. However, the side effects of radiotherapy are associated with significant morbidity and mortality that impact patients' qual-

ity of life.[65] Radiation enteritis is a common complication of radiotherapy for abdominal and pelvic tumors, often manifesting as abdominal pain, diarrhea, and rectal bleeding, which are prone to recurrence and poorly responsive to traditional treatments.[66] In a case report, a 64-year-old female with cervical cancer and chronic radiation enteritis underwent two courses of FMT and then experienced short- and long-term relief from symptoms without adverse effects.[67] In a pilot study, FMT was performed on five patients with chronic radiation enteritis who were unresponsive to conventional treatment. Healthy donor gut microbiota was transplanted into the patients, and the patients' radiation toxicity, gastrointestinal symptoms, and changes in gut microbiota were regularly evaluated. After eight weeks, three patients showed improvement, one underwent surgery for other reasons, and one showed no improvement, with no FMT-related deaths or infectious complications.[68] In a prospective cohort study, researchers treated 20 patients with radiation enteritis complicated by intestinal obstruction with FMT and followed them up for six months.[69] Compared to the conventional treatment group (25 patients), the FMT group showed superior gastrointestinal quality of life scores, body mass index, total protein, and albumin levels, effectively improving the patients' early nutritional status and quality of life.[69] Another study involving 127 patients with radiation enteritis treated with FMT showed clinical cure rates of 61.4%, 56.5%, and 47.6% at three, 12, and 36 months, respectively.[70]

FMT and immunotherapy

The unique immune-suppressive microenvironment and low immunogenicity of PDAC make it challenging for immunotherapy to achieve desirable outcomes.[71–73] Improving responses to immunotherapy and developing effective immunotherapeutic strategies remain long-term tasks. Increasing evidence suggests that gut microbiota modulation plays a significant role in cancer immunotherapy.[74] For example, the gut microbiota metabolite trimethylamine-N-oxide has immunomodulatory effects and can enhance the sensitivity of PDAC to immune checkpoint inhibitors.[33] Compared to tumor patients who did not receive antibiotic treatment before and after their first PD-1/PD-L1 treatment, the group receiving antibiotic treatment showed significantly shortened progression-free survival and overall survival.[43,75] Moreover, immune checkpoint inhibitor-induced colitis, an adverse effect of immunotherapy treatment, could be ameliorated by FMT.[76,77] Although there are no clinical studies on FMT for immunotherapy in PDAC, initial successes have been achieved in immunotherapy for other cancers. Several FMT clinical trials have shown that transplanting gut microbiota from immunotherapy responders can reverse tumor resistance to PD-1/PD-L1 treatment,[55,78,79] and healthy individuals as donors can also reverse the refractoriness of tumors to immunotherapy.[80,81]

Based on the above research, combining FMT with existing therapies such as chemotherapy, radiotherapy, and immunotherapy holds promise for improving treatment efficiency and reducing side effects. Previous research on FMT in cancer treatment has primarily concentrated on its combination with immunotherapy, chemotherapy, and radiation therapy. The neoadjuvant therapy and perioperative periods may also present opportune times for combining FMT with treatment in the future, as earlier modulation of gut microbiota, immune function, and nutritional status in cancer patients could potentially enhance therapeutic outcomes against tumors. Although there is currently no publicly available clinical data on FMT for PDAC treatment, the enormous potential of FMT in treating PDAC cannot be denied. Several clinical trials are currently underway. In one preliminary study, researchers initiated FMT treatment four weeks before Whipple surgery for PDAC patients (NCT04975217). Other clinical trials are exploring the application of FMT in the treatment of advanced PDAC (ChiCTR2100049431) (Table 1).

Current issues in FMT treatment for PDAC

Complications of FMT treatment

Although FMT is recognized as a safe and low-risk medical innovation, it still carries the risk of complications. In a previous report, two recipients of FMT developed bacteremia caused by extended-spectrum beta-lactamase-producing Escherichia coli, with both cases linked to the same stool donor. One of the patients died, which was attributed to the donor not undergoing screening for multidrug resistance.[82] Therefore, ensuring the safety of transplant materials is crucial for the safety profile of FMT. Currently, guidelines and consensus on FMT have been developed, outlining donor screening and management protocols, as well as requirements for the preparation and quality control of transplant materials. Enhancing donor screening and daily management is a critical measure to ensure the quality and safety of transplants. Before FMT, a comprehensive assessment of the donor's recent health status is necessary, including medical history, clinical symptoms, blood tests, fecal microbial tests, and lifestyle and dietary habits. Additionally, cohabitation is an important factor in the transmission of microbes, with the median strain-sharing rates of gut and oral microbiota among cohabiting individuals being 12% and 32%, respectively. The impact of cohabitation duration on strain sharing is greater than that of age and genetics.[83,84] Therefore, it may also be necessary to focus on the gut microbiota health of cohabitants in the future. A systematic review of 129 FMT-related studies conducted from 2000 to 2020 found that most FMT-related adverse events were mild or moderate and self-limiting. The most common adverse events were diarrhea (10%) and abdominal discomfort/pain/cramping (7%); 1.4% of FMT recipients experienced severe adverse events, all related to mucosal barrier damage.[85] Thus, an accurate evaluation of the recipient's tolerance for FMT is essential before proceeding with the procedure. Moreover, selecting an appropriate route of FMT delivery, enhancing donor screening before transplantation, and regularly monitoring recipients throughout the process may help reduce risks to some extent.

Challenges and unresolved issues in FMT

FMT presents a double-edged sword, with potential risks of transmitting harmful microorganisms alongside the benefits of improving gut microbiota, underscoring the critical importance of establishing implementation guidelines. With its widespread application, FMT protocols have been established across different regions, but specific details have not been standardized. Donor screening and management are among the most challenging aspects of FMT implementation and are crucial factors affecting the safety and efficacy of the procedure. Strict donor screening criteria result in a screening success rate of only 1.7%, which is far from meeting clinical demands.[86] Additionally, rules for donor-recipient matching are still under exploration, and further discussion is needed on how to select suitable donors based on recipient-specific factors to maximize therapeutic effects. For example, should the recipient's gut microbiota characteristics be considered? Could the diversity of the recipient's gut microbiota potentially influence the outcomes of FMT? Donor–recipient enterotype matching and

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Table 1. The registered clinical trials about the therapeutic effects of fecal microbiota transplantation (FMT) in cancer

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
Microbiota transplant to cancer patients who have failed immunotherapy using feces from clinical responders	NCT05286294	Melanoma; head and neck squamous cell carcinoma; cutaneous squamous cell carcinoma; clear cell renal cell carcinoma; non-small cell lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	20	RECRUITING
Washed microbiota transplantation for the treatment of oncotherapy-related intestinal complications	NCT04721041	Cancer	INTERVENTIONAL	SINGLE_GROUP	/	40	RECRUITING
Utilization of microbiome as biomarkers and therapeutics in immuno-oncology	NCT04264975	Solid carcinoma	INTERVENTIONAL	SINGLE_GROUP	/	60	UNKNOWN
FMT in treating immune-checkpoint inhibitor induced-diarrhea or colitis in genitourinary cancer patients	NCT04038619	Malignant genitourinary system neoplasm; melanoma; lung cancer; ovarian cancer; uterine cancer; breast cancer; cervical cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE1	40	RECRUITING
FMT in checkpoint inhibitor-mediated diarrhea and colitis	NCT06206707	Malignant melanoma; kidney cancer	INTERVENTIONAL	PARALLEL; Masking: DOUBLE (PARTICIPANT, INVESTIGATOR)	/	20	RECRUITING
FMT in patients with malignancies not responding to cancer immunotherapy	NCT05273255	Cancer	INTERVENTIONAL	SINGLE_GROUP	/	30	RECRUITING
Efficacy and safety of FMT in reducing recurrence of colorectal adenoma	NCT06205862	Colorectal adenoma	INTERVENTIONAL	PARALLEL; Masking: DOUBLE (PARTICIPANT, INVESTIGATOR)	PHASE2	466	RECRUITING
FMT in metastatic melanoma patients who failed immunotherapy	NCT03353402	Melanoma	INTERVENTIONAL	SINGLE_GROUP	PHASE1	40	UNKNOWN
Preventing toxicity in renal cancer patients treated with immunotherapy using FMT	NCT04163289	Renal cell carcinoma	INTERVENTIONAL	SINGLE_GROUP	PHASE1	20	ACTIVE_NOT_RECRUITING
FMT with immune checkpoint inhibitors in lung cancer	NCT05502913	Metastatic lung cancer	INTERVENTIONAL	PARALLEL; Masking: QUADRUPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR, OUTCOMES_ASSESSOR)	PHASE2	80	RECRUITING
FMT in melanoma patients	NCT03341143	Melanoma	INTERVENTIONAL	SINGLE_GROUP	PHASE2	18	ACTIVE_NOT_RECRUITING

(continued)

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Table 1. *(continued)*

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
Inducing remission in melanoma patients with Checkpoint Inhibitor therapy using FMT.	NCT04577729	Malignant melanoma	INTERVENTIONAL	PARALLEL; Masking: DOUBLE (PARTICIPANT, INVESTIGATOR)	/	5	TERMINATED
FMT to convert the response to immunotherapy	NCT05251389	Melanoma	INTERVENTIONAL	PARALLEL; Masking: QUADRUPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR, OUTCOMES_ASSESSOR)	PHASE2	24	RECRUITING
FMT and pembrolizumab for men with metastatic castration-resistant prostate cancer.	NCT04116775	Prostate cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	32	UNKNOWN
Chemotherapy and stool transplant in pancreatic ductal adenocarcinoma (PDAC)	NCT06393400	Unresectable or metastatic advanced pancreatic ductal adenocarcinoma	INTERVENTIONAL	SINGLE_GROUP	PHASE1	20	NOT_YET_ RECRUITING
FMT in patients with advanced gastric cancer	NCT06346093	Advanced gastric cancer	INTERVENTIONAL	PARALLEL; Masking: DOUBLE (PARTICIPANT, INVESTIGATOR)	/	66	RECRUITING
A single dose FMT infusion as an adjunct to Keytruda for metastatic mesothelioma	NCT04056026	Mesothelioma	INTERVENTIONAL	SINGLE_GROUP	EARLY_ PHASE1	1	COMPLETED
FMT in diarrhea induced by tyrosine-kinase inhibitors	NCT04040712	Renal cell cancer	INTERVENTIONAL	PARALLEL; Masking: TRIPLE (PARTICIPANT, CARE_PROVIDER, OUTCOMES_ASSESSOR)	/	20	COMPLETED
FMT for the treatment of pancreatic cancer	NCT04975217	Pancreatic ductal adenocarcinoma	INTERVENTIONAL	SINGLE_GROUP	EARLY_ PHASE1	10	RECRUITING
Microbiota transplant in advanced lung cancer treated with immunotherapy	NCT04924374	Lung cancer	INTERVENTIONAL	PARALLEL; Masking: NONET	/	20	RECRUITING
Prevention of dysbiosis complications with autologous FMT in AML patients	NCT02928523	Leukemia, myeloid, acute	INTERVENTIONAL	SINGLE_GROUP	PHASE2	20	COMPLETED
Fecal microbiota transfer in liver cancer to overcome resistance to atezolizumab/bevacizumab	NCT05690048	Immunotherapy	INTERVENTIONAL	PARALLEL; Masking: SINGLE (PARTICIPANT)	PHASE2	48	NOT_YET_ RECRUITING

(continued)

Table 1. *(continued)*

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
FMT and re-introduction of anti-programmed death 1 (anti-PD-1) therapy (Pembrolizumab or Nivolumab) for the treatment of metastatic colorectal cancer in anti-PD-1 non-responders	NCT04729322	Metastatic colorectal adenocarcinoma	INTERVENTIONAL	PARALLEL; Masking: NONE	PHASE2	15	ACTIVE_NOT_RECRUITING
FMT capsule for improving the efficacy of anti-PD-1	NCT04130763	Gastrointestinal system cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE1	10	ACTIVE_NOT_RECRUITING
FMT+chemotherapy+Sintilimab as first-line treatment for advanced gastric cancer	NCT06405113	Gastric cancer	INTERVENTIONAL	PARALLEL; Masking: TRIPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR)	PHASE2	198	NOT_YET_RECRUITING
FMT with nivolumab in patients with advanced solid cancers who have progressed during anti-PD-1 therapy	NCT05533983	Solid carcinoma	INTERVENTIONAL	SINGLE_GROUP	/	50	NOT_YET_RECRUITING
Responder-derived FMT (R-FMT) and pembrolizumab in relapsed/refractory programmed death ligand 1 (PD-L1) positive non-small cell lung cancer	NCT05669846	Non-small cell lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	26	NOT_YET_RECRUITING
A study of FMT in patients with acute myeloid leukemia allogeneic hematopoietic cell transplantation in recipients	NCT03678493	Acute myeloid leukemia	INTERVENTIONAL	PARALLEL; Masking: NONE	PHASE2	100	COMPLETED
FMT combined with immune checkpoint inhibitor and tyrosine kinase inhibitors in the treatment of colorectal cancer patients with advanced stage	NCT05279677	Colorectal neoplasms malignant	INTERVENTIONAL	SINGLE_GROUP	PHASE2	30	UNKNOWN
Intestinal microbiota transplant prior to allogeneic stem cell transplant trial	NCT06355583	Acute lymphoblastic leukemia	INTERVENTIONAL	PARALLEL; Masking: TRIPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR)	PHASE2	50	NOT_YET_RECRUITING
Pilot trial of FMT for lymphoma patients receiving axicabtagene ciloleucel therapy.	NCT06218602	Lymphoma	INTERVENTIONAL	SINGLE_GROUP	PHASE2	40	RECRUITING
FMT+immunotherapy+chemotherapy as first-line treatment for driver-gene negative advanced non-small cell lung cancer	NCT06403111	Non-small cell lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	62	NOT_YET_RECRUITING

(continued)

Table 1. *(continued)*

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
Role of the gut microbiome and fecal transplant on medication-induced gastrointestinal complications in patients with cancer	NCT03819296	Melanoma	INTERVENTIONAL	SINGLE_GROUP	PHASE2	800	RECRUITING
Assessing the tolerance and clinical benefit of fecal transplantation in patients with melanoma	NCT04988841	Melanoma	INTERVENTIONAL	PARALLEL; Masking: QUADRUPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR, OUTCOMES_ASSESSOR)	PHASE2	60	RECRUITING
FMT to improve efficacy of immune checkpoint inhibitors in renal cell carcinoma	NCT04758507	Renal cell carcinoma	INTERVENTIONAL	PARALLEL; Masking: QUADRUPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR, OUTCOMES_ASSESSOR)	PHASE2	50	ACTIVE_NOT_RECRUITING
Gut microbiota reconstruction for immunotherapy	NCT05008861	Non-small cell lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE1	20	UNKNOWN
Impact of oral nutritional supplements on patients undergoing hematopoietic stem cell transplantation	NCT05460013	Hematological malignancy	INTERVENTIONAL	PARALLEL; Masking: SINGLE (PARTICIPANT)	NA	100	RECRUITING
RBX7455 before surgery for the treatment of operable breast cancer	NCT04139993	Breast cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE1	3	TERMINATED
FMT combined with atezolizumab plus bevacizumab in patients with hepatocellular carcinoma who failed to respond to prior immunotherapy	NCT05750030	Hepatocellular carcinoma	INTERVENTIONAL	SINGLE_GROUP	PHASE2	12	RECRUITING
Pembrolizumab/Lenvatinib with and without responder-derived FMT in relapsed/refractory melanoma	NCT06030037	PD-1 refractory advanced melanoma	INTERVENTIONAL	PARALLEL; Masking: NONE	PHASE2	56	NOT_YET_RECRUITING
Oral immunonutrition with synbiotics, Omega 3, and vitamin D in patients undergoing duodenopancreatectomy for tumoral lesion.	NCT05271344	Pancreatic cancer	INTERVENTIONAL	PARALLEL; Masking: TRIPLE (PARTICIPANT, INVESTIGATOR, OUTCOMES_ASSESSOR)	/	74	RECRUITING
Feasibility study of microbial ecosystem therapeutics to evaluate effects of fecal microbiome in patients on immunotherapy	NCT03686202	All solid tumors	INTERVENTIONAL	SINGLE_GROUP	PHASE2	65	ACTIVE_NOT_RECRUITING

(continued)

Table 1. *(continued)*

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
Role of microbiome as a biomarker in locoregionally-advanced oropharyngeal squamous cell carcinoma 2	NCT03838601	Head and neck squamous cell carcinoma	INTERVENTIONAL	SINGLE_GROUP	/	30	ACTIVE_NOT_RECRUITING
Microbiota and pancreatic cancer cachexia	NCT05606523	Pancreatic cancer	OBSERVATIONAL	Observational Model	/	24	RECRUITING
Role of gut microbiome in cancer therapy	NCT05112614	Hematopoietic and lymphoid cell neoplasm; malignant solid neoplasm	OBSERVATIONAL	Observational Model	/	5,000	RECRUITING
The effect of gut microbiota on postoperative liver function recovery in patients with hepatocellular carcinoma	NCT04303286	Hepatocellular carcinoma	OBSERVATIONAL	Observational Model	/	200	COMPLETED
The gut microbiome in acute myeloid leukemia with FLT3 mutation undergoing allogeneic hematopoietic stem cell transplantation with or without sorafenib maintenance	NCT05601895	Acute leukemia	OBSERVATIONAL	Observational Model	/	60	RECRUITING
The mechanism of enhancing the anti-tumor effects of chimeric antigen receptor T-cell immunotherapy on pancreatic cancer by gut microbiota regulation	NCT04203459	Pancreatic cancer	OBSERVATIONAL	Observational Model	/	80	UNKNOWN
The gut microbiome in acute myeloid leukemia with FMS-like tyrosine kinase-3/internal tandem duplication (FLT3/ITD) mutation undergoing allogeneic hematopoietic stem cell transplantation with or without sorafenib maintenance after allogeneic hematopoietic stem cell transplantation	NCT05596981	Acute myeloid leukemia with FLT3/ITD mutation	OBSERVATIONAL	Observational Model	/	60	RECRUITING
The gut microbiome and sorafenib maintenance therapy in FLT3/ITD positive cute myeloid leukemia after allogeneic hematopoietic stem cell transplantation	NCT05596968	Acute myeloid leukemia with FLT3/ITD mutation	OBSERVATIONAL	Observational Model	/	37	RECRUITING
Multiple myeloma outcomes based on maintenance therapy post autologous stem cell transplant	NCT05271630	Multiple myeloma	OBSERVATIONAL	Observational Model	/	69	RECRUITING
Fecal bacteria transplantation in the treatment of patients with advanced cancer	ChiCTR2100049431	Liver, colon, gastric, pancreatic, and lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	50	UNKNOWN

complementarity may contribute to the colonization of microbiota and the outcomes of FMT.[87,88] FMT transplant materials include liquid and capsule forms, with administration methods including upper gastrointestinal tract liquid injection, lower gastrointestinal tract liquid injection, and oral capsules. Currently, there is a lack of comparative studies on the efficacy of different administration methods in tumor patients, and no consensus exists on the optimal dosage for FMT. The infusion dosage, frequency, and duration of FMT treatment may vary considerably across different diseases and patients. In theory, greater quantities of donor microbes can enhance colonization of the recipient's gut, achievable through either increasing the microbial amounts per single FMT or the frequency of administration. In many clinical studies, long-term and repeated FMT have been considered more favorable for outcomes.[89–93] Therefore, a considerable number of clinical trials are still needed to further address these issues.

Conclusions

It is increasingly recognized that the intricate relationship between the gut microbiota and PDAC underscores the potential of microbiome-based strategies in the management of this devastating disease. The identification of specific microbial signatures associated with PDAC offers a promising avenue for the development of non-invasive diagnostic tools. These tools could facilitate early detection, thereby improving patient prognosis through timely intervention. Moreover, the modulation of the gut microbiota through targeted interventions, such as fecal microbiota transplantation, presents a novel therapeutic approach that could enhance the efficacy of current treatments and potentially alleviate treatment-related adverse effects. Nevertheless, FMT also faces numerous challenges, such as dosage optimization, patient acceptance, and the scientific matching of donors and recipients. Multiple exploration gaps remain in the FMT validity and its long-term consequences. However, for microbiota-based strategies to become more practical in clinical applications, there is still a long way to go.

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Conflict of interest

The authors report that there are no competing interests to declare.

Author contributions

Study concept and design, acquisition of the data, drafting of the manuscript (XH, CM), critical revision of the manuscript (XK). All authors have made a significant contribution to this study and have approved the final manuscript.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021;71(1):7–33. doi:10.3322/caac.21654, PMID:33946.

[2] Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. Therapeutic developments in pancreatic cancer: current and future perspectives. Nat Rev Gastroenterol Hepatol 2018;15(6):333–348. doi:10.1038/s41575-018-0005-x, PMID:29717230.

[3] Pourali G, Kazemi D, Chadeganipour AS, Arastonejad M, Kashani SN, Pourali R, *et al*. Microbiome as a biomarker and therapeutic target in pancreatic cancer. BMC Microbiol 2024;24(1):16. doi:10.1186/s12866-023-03166-4, PMID:38183010.

[4] Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science 2005;307(5717):1915–1920. doi:10.1126/science.1104816, PMID:15790844.

[5] Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA. The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. Cancer Cell 2018;33(4):570–580. doi:10.1016/j.ccell.2018.03.015, PMID:29634945.

[6] Thomas RM, Jobin C. Microbiota in pancreatic health and disease: the next frontier in microbiome research. Nat Rev Gastroenterol Hepatol 2020;17(1):53–64. doi:10.1038/s41575-019-0242-7, PMID:31811279.

[7] Chandra V, McAllister F. Therapeutic potential of microbial modulation in pancreatic cancer. Gut 2021;70(8):1419–1425. doi:10.1136/gutjnl-2019-319807, PMID:33906958.

[8] Pandya G, Kirtonia A, Singh A, Goel A, Mohan CD, Rangappa KS, *et al*. A comprehensive review of the multifaceted role of the microbiota in human pancreatic carcinoma. Semin Cancer Biol 2022;86(Pt 3):682–692. doi:10.1016/j.semcancer.2021.05.027, PMID:34051351.

[9] Ting NL, Lau HC, Yu J. Cancer pharmacomicrobiomics: targeting microbiota to optimise cancer therapy outcomes. Gut 2022;71(7):1412–1425. doi:10.1136/gutjnl-2021-326264, PMID:35277453.

[10] Chen D, Wu J, Jin D, Wang B, Cao H. Fecal microbiota transplantation in cancer management: Current status and perspectives. Int J Cancer 2019;145(8):2021–2031. doi:10.1002/ijc.32003, PMID:30458058.

[11] Brody H. The gut microbiome. Nature 2020;577(7792):S5. doi:10.1038/d41586-020-00194-2, PMID:31996824.

[12] Fassarella M, Blaak EE, Penders J, Nauta A, Smidt H, Zoetendal EG. Gut microbiome stability and resilience: elucidating the response to perturbations in order to modulate gut health. Gut 2021;70(3):595–605. doi:10.1136/gutjnl-2020-321747, PMID:33051190.

[13] Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. Nature 2012;489(7415):242–249. doi:10.1038/nature11552, PMID:22972297.

[14] Guigoz Y, Doré J, Schiffrin EJ. The inflammatory status of old age can be nurtured from the intestinal environment. Curr Opin Clin Nutr Metab Care 2008;11(1):13–20. doi:10.1097/MCO.0b013e3282f2bfdf, PMID:18090652.

[15] Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, *et al*. Enterotypes of the human gut microbiome. Nature 2011;473(7346):174–180. doi:10.1038/nature09944, PMID:21508958.

[16] Wei MY, Shi S, Liang C, Meng QC, Hua J, Zhang YY, *et al*. The microbiota and microbiome in pancreatic cancer: more influential than expected. Mol Cancer 2019;18(1):97. doi:10.1186/s12943-019-1008-0, PMID:31109338.

[17] Nagata N, Nishijima S, Kojima Y, Hisada Y, Imbe K, Miyoshi-Akiyama T, *et al*. Metagenomic Identification of Microbial Signatures Predicting Pancreatic Cancer From a Multinational Study. Gastroenterology 2022;163(1):222–238. doi:10.1053/j.gastro.2022.03.054, PMID:35398347.

[18] Zhou W, Zhang D, Li Z, Jiang H, Li J, Ren R, *et al*. The fecal microbiota of patients with pancreatic ductal adenocarcinoma and autoimmune pancreatitis characterized by metagenomic sequencing. J Transl Med 2021;19(1):215. doi:10.1186/s12967-021-02882-7, PMID:34006295.

[19] Lindkvist B, Johansen D, Borgström A, Manjer J. A prospective study of Helicobacter pylori in relation to the risk for pancreatic cancer. BMC Cancer 2008;8:321. doi:10.1186/1471-2407-8-321, PMID:18986545.

[20] Guo Y, Liu W, Wu J. Helicobacter pylori infection and pancreatic cancer risk: A meta-analysis. J Cancer Res Ther 2016;12(Supplement):C229–C232. doi:10.4103/0973-1482.200744, PMID:28230023.

[21] Kartal E, Schmidt TSB, Molina-Montes E, Rodríguez-Perales S, Wirbel J, Maistrenko OM, *et al*. A faecal microbiota signature with high specificity for pancreatic cancer. Gut 2022;71(7):1359–1372.

doi:10.1136/gutjnl-2021-324755, PMID:35260444.
[22] Yang J, Ma Y, Tan Q, Zhou B, Yu D, Jin M, *et al*. Gut Streptococcus is a microbial marker for the occurrence and liver metastasis of pancreatic cancer. Front Microbiol 2023;14:1184869. doi:10.3389/fmicb.2023.1184869, PMID:37389332.
[23] Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. Nat Rev Immunol 2016;16(6):341–352. doi:10.1038/nri.2016.42, PMID:27231050.
[24] Buscail L, Bournet B, Cordelier P. Role of oncogenic KRAS in the diagnosis, prognosis and treatment of pancreatic cancer. Nat Rev Gastroenterol Hepatol 2020;17(3):153–168. doi:10.1038/s41575-019-0245-4, PMID:32005945.
[25] Ikebe M, Kitaura Y, Nakamura M, Tanaka H, Yamasaki A, Nagai S, *et al*. Lipopolysaccharide (LPS) increases the invasive ability of pancreatic cancer cells through the TLR4/MyD88 signaling pathway. J Surg Oncol 2009;100(8):725–731. doi:10.1002/jso.21392, PMID:19722233.
[26] Sethi V, Kurtom S, Tarique M, Lavania S, Malchiodi Z, Hellmund L, *et al*. Gut Microbiota Promotes Tumor Growth in Mice by Modulating Immune Response. Gastroenterology 2018;155(1):33–37.e6. doi:10.1053/j.gastro.2018.04.001, PMID:29630898.
[27] Pushalkar S, Hundeyin M, Daley D, Zambirinis CP, Kurz E, Mishra A, *et al*. The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression. Cancer Discov 2018;8(4):403–416. doi:10.1158/2159-8290.CD-17-1134, PMID:29567829.
[28] Alam A, Levanduski E, Denz P, Villavicencio HS, Bhatta M, Alhorebi L, *et al*. Fungal mycobiome drives IL-33 secretion and type 2 immunity in pancreatic cancer. Cancer Cell 2022;40(2):153–167.e11. doi:10.1016/j.ccell.2022.01.003, PMID:35120601.
[29] Panebianco C, Villani A, Pisati F, Orsenigo F, Ulaszewska M, Latiano TP, *et al*. Butyrate, a postbiotic of intestinal bacteria, affects pancreatic cancer and gemcitabine response in in vitro and in vivo models. Biomed Pharmacother 2022;151:113163. doi:10.1016/j.biopha.2022.113163, PMID:35617803.
[30] Farrow B, Rychahou P, O'Connor KL, Evers BM. Butyrate inhibits pancreatic cancer invasion. J Gastrointest Surg 2003;7(7):864–870. doi:10.1007/s11605-003-0031-y, PMID:14592659.
[31] Bloom EJ, Siddiqui B, Hicks JW, Kim YS. Effect of sodium butyrate, a differentiating agent, on cell surface glycoconjugates of a human pancreatic cell line. Pancreas 1989;4(1):59–64. doi:10.1097/00006676-198902000-00009, PMID:2717602.
[32] Tintelnot J, Xu Y, Lesker TR, Schönlein M, Konczalla L, Giannou AD, *et al*. Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer. Nature 2023;615(7950):168–174. doi:10.1038/s41586-023-05728-y, PMID:36813961.
[33] Mirji G, Worth A, Bhat SA, El Sayed M, Kannan T, Goldman AR, *et al*. The microbiome-derived metabolite TMAO drives immune activation and boosts responses to immune checkpoint blockade in pancreatic cancer. Sci Immunol 2022;7(75):eabn0704. doi:10.1126/sciimmunol.abn0704, PMID:36083892.
[34] Totiger TM, Srinivasan S, Jala VR, Lamichhane P, Dosch AR, Gaidarski AA 3rd, *et al*. Urolithin A, a Novel Natural Compound to Target PI3K/AKT/mTOR Pathway in Pancreatic Cancer. Mol Cancer Ther 2019;18(2):301–311. doi:10.1158/1535-7163.MCT-18-0464, PMID:30404927.
[35] Giordano SH, Elias AD, Gradishar WJ. NCCN Guidelines Updates: Breast Cancer. J Natl Compr Canc Netw 2018;16(5S):605–610. doi:10.6004/jnccn.2018.0043, PMID:29784737.
[36] Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, *et al*. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Science 2017;357(6356):1156–1160. doi:10.1126/science.aah5043, PMID:28912244.
[37] Nagar S, Blanchard RL. Pharmacogenetics of uridine diphosphoglucuronosyltransferase (UGT) 1A family members and its role in patient response to irinotecan. Drug Metab Rev 2006;38(3):393–409. doi:10.1080/03602530600739835, PMID:16877259.
[38] Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management. Ther Adv Med Oncol 2010;2(1):51–63. doi:10.1177/1758834009355164, PMID:21789126.
[39] Tobin PJ, Dodds HM, Clarke S, Schnitzler M, Rivory LP. The relative contributions of carboxylesterase and beta-glucuronidase in the formation of SN-38 in human colorectal tumours. Oncol Rep 2003;10(6):1977–1979. PMID:14534729.
[40] Anthony WE, Wang B, Sukhum KV, D'Souza AW, Hink T, Cass C, *et al*. Acute and persistent effects of commonly used antibiotics on the gut microbiome and resistome in healthy adults. Cell Rep 2022;39(2):110649. doi:10.1016/j.celrep.2022.110649, PMID:35417701.
[41] Pederzoli F, Riba M, Venegoni C, Marandino L, Bandini M, Alchera E, *et al*. Stool Microbiome Signature Associated with Response to Neoadjuvant Pembrolizumab in Patients with Muscle-invasive Bladder Cancer. Eur Urol 2024;85(5):417–421. doi:10.1016/j.eururo.2023.12.014, PMID:38184414.
[42] Cortellini A, Ricciuti B, Facchinetti F, Alessi JVM, Venkatraman D, Dall'Olio FG, *et al*. Antibiotic-exposed patients with non-small-cell lung cancer preserve efficacy outcomes following first-line chemoimmunotherapy. Ann Oncol 2021;32(11):1391–1399. doi:10.1016/j.annonc.2021.08.1744, PMID:34400292.
[43] Kim CG, Koh JY, Shin SJ, Shin JH, Hong M, Chung HC, *et al*. Prior antibiotic administration disrupts anti-PD-1 responses in advanced gastric cancer by altering the gut microbiome and systemic immune response. Cell Rep Med 2023;4(11):101251. doi:10.1016/j.xcrm.2023.101251, PMID:37890486.
[44] Park JS, Gazzaniga FS, Wu M, Luthens AK, Gillis J, Zheng W, *et al*. Targeting PD-L2-RGMb overcomes microbiome-related immunotherapy resistance. Nature 2023;617(7960):377–385. doi:10.1038/s41586-023-06026-3, PMID:37138075.
[45] Schmitt FCF, Brenner T, Uhle F, Loesch S, Hackert T, Ulrich A, *et al*. Gut microbiome patterns correlate with higher postoperative complication rates after pancreatic surgery. BMC Microbiol 2019;19(1):42. doi:10.1186/s12866-019-1399-5, PMID:30777006.
[46] Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? Am J Gastroenterol 2012;107(11):1755. doi:10.1038/ajg.2012.251, PMID:23160295.
[47] Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, *et al*. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol 2013;108(4):478–498. doi:10.1038/ajg.2013.4, PMID:23439232.
[48] Lopetuso LR, Deleu S, Godny L, Petito V, Puca P, Facciotti F, *et al*. The first international Rome consensus conference on gut microbiota and faecal microbiota transplantation in inflammatory bowel disease. Gut 2023;72(9):1642–1650. doi:10.1136/gutjnl-2023-329948, PMID:37339849.
[49] Costello SP, Hughes PA, Waters O, Bryant RV, Vincent AD, Blatchford P, *et al*. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. JAMA 2019;321(2):156–164. doi:10.1001/jama.2018.20046, PMID:30644982.
[50] Holvoet T, Joossens M, Vázquez-Castellanos JF, Christiaens E, Heyerick L, Boelens J, *et al*. Fecal Microbiota Transplantation Reduces Symptoms in Some Patients With Irritable Bowel Syndrome With Predominant Abdominal Bloating: Short- and Long-term Results From a Placebo-Controlled Randomized Trial. Gastroenterology 2021;160(1):145–157.e8. doi:10.1053/j.gastro.2020.07.013, PMID:32681922.
[51] Ianiro G, Rossi E, Thomas AM, Schinzari G, Masucci L, Quaranta G, *et al*. Faecal microbiota transplantation for the treatment of diarrhoea induced by tyrosine-kinase inhibitors in patients with metastatic renal cell carcinoma. Nat Commun 2020;11(1):4333. doi:10.1038/s41467-020-18127-y, PMID:32859933.
[52] Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, *et al*. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome 2017;5(1):10. doi:10.1186/s40168-016-0225-7, PMID:28122648.
[53] Vendrik KEW, Ooijevaar RE, de Jong PRC, Laman JD, van Oosten BW, van Hilten JJ, *et al*. Fecal Microbiota Transplantation in Neurological Disorders. Front Cell Infect Microbiol 2020;10:98. doi:10.3389/fcimb.2020.00098, PMID:32266160.
[54] Allegretti JR, Kassam Z, Mullish BH, Chiang A, Carrellas M, Hurtado J, *et al*. Effects of Fecal Microbiota Transplantation With Oral Capsules

in Obese Patients. Clin Gastroenterol Hepatol 2020;18(4):855–863.e2. doi:10.1016/j.cgh.2019.07.006, PMID:31301451.
[55] Routy B, Lenehan JG, Miller WH Jr, Jamal R, Messaoudene M, Daisley BA, *et al*. Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial. Nat Med 2023;29(8):2121–2132. doi:10.1038/s41591-023-02453-x, PMID:37414899.
[56] Cammarota G, Ianiro G, Kelly CR, Mullish BH, Allegretti JR, Kassam Z, *et al*. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut 2019;68(12):2111–2121. doi:10.1136/gutjnl-2019-319548, PMID:31563878.
[57] Cammarota G, Ianiro G, Tilg H, Rajilić-Stojanović M, Kump P, Satokari R, *et al*. European consensus conference on faecal microbiota transplantation in clinical practice. Gut 2017;66(4):569–580. doi:10.1136/gutjnl-2016-313017, PMID:28087657.
[58] Huang J, Zhou H, Song T, Wang B, Ge H, Zhang D, *et al*. Fecal microbiota transplantation from sodium alginate-dosed mice and normal mice mitigates intestinal barrier injury and gut dysbiosis induced by antibiotics and cyclophosphamide. Food Funct 2023;14(12):5690–5701. doi:10.1039/d3fo01193c, PMID:37272879.
[59] Lui JB, Devarajan P, Teplicki SA, Chen Z. Cross-differentiation from the CD8 lineage to CD4 T cells in the gut-associated microenvironment with a nonessential role of microbiota. Cell Rep 2015;10(4):574–585. doi:10.1016/j.celrep.2014.12.053, PMID:25640181.
[60] Mager LF, Burkhard R, Pett N, Cooke NCA, Brown K, Ramay H, *et al*. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. Science 2020;369(6510):1481–1489. doi:10.1126/science.abc3421, PMID:32792462.
[61] Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, *et al*. Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes. Cell 2019;178(4):795–806.e12. doi:10.1016/j.cell.2019.07.008, PMID:31398337.
[62] Catenacci DV, Junttila MR, Karrison T, Bahary N, Horiba MN, Nattam SR, *et al*. Randomized Phase Ib/II Study of Gemcitabine Plus Placebo or Vismodegib, a Hedgehog Pathway Inhibitor, in Patients With Metastatic Pancreatic Cancer. J Clin Oncol 2015;33(36):4284–4292. doi:10.1200/JCO.2015.62.8719, PMID:26527777.
[63] Amrutkar M, Gladhaug IP. Pancreatic Cancer Chemoresistance to Gemcitabine. Cancers (Basel) 2017;9(11):157. doi:10.3390/cancers9110157, PMID:29144412.
[64] Alexander JL, Wilson ID, Teare J, Marchesi JR, Nicholson JK, Kinross JM. Gut microbiota modulation of chemotherapy efficacy and toxicity. Nat Rev Gastroenterol Hepatol 2017;14(6):356–365. doi:10.1038/nrgastro.2017.20, PMID:28270698.
[65] Grimes DR. Radiofrequency Radiation and Cancer: A Review. JAMA Oncol 2022;8(3):456–461. doi:10.1001/jamaoncol.2021.5964, PMID:34882171.
[66] Erratum to "MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy". Cancer 2021;127(19):3700. doi:10.1002/cncr.33549, PMID:34233011.
[67] Wang L, Li Y, Zhang YJ, Peng LH. Intestinal microecological transplantation for a patient with chronic radiation enteritis: A case report. World J Gastroenterol 2024;30(19):2603–2611. doi:10.3748/wjg.v30.i19.2603, PMID:38817661.
[68] Ding X, Li Q, Li P, Chen X, Xiang L, Bi L, *et al*. Fecal microbiota transplantation: A promising treatment for radiation enteritis? Radiother Oncol 2020;143:12–18. doi:10.1016/j.radonc.2020.01.011, PMID:32044171.
[69] Cui JQ, Tian HL, Wang XJ, Wang L, Liu YK, Ye C, *et al*. [Analysis of short-term efficacy of perioperative fecal microbiota transplantation combined with nutritional support in patients with radiation-induced enteritis complicated by intestinal obstruction]. Zhonghua Wei Chang Wai Ke Za Zhi 2023;26(10):955–962. doi:10.3760/cma.j.cn441530-20230816-00052.
[70] Li N, Tian HL, Chen QY, Yang B, Ma CL, Chen ZL, *et al*. [Efficacy analysis of fecal microbiota transplantation in the treatment of 2010 patients with intestinal disorders]. Zhonghua Wei Chang Wai Ke Za Zhi 2019;22(9):861–868. doi:10.3760/cma.j.issn.1671-0274.2019.09.011.
[71] Vonderheide RH, Bayne LJ. Inflammatory networks and immune surveillance of pancreatic carcinoma. Curr Opin Immunol 2013;25(2):200–205. doi:10.1016/j.coi.2013.01.006, PMID:23422836.
[72] Balli D, Rech AJ, Stanger BZ, Vonderheide RH. Immune Cytolytic Activity Stratifies Molecular Subsets of Human Pancreatic Cancer. Clin Cancer Res 2017;23(12):3129–3138. doi:10.1158/1078-0432.CCR-16-2128, PMID:28007776.
[73] Stromnes IM, Hulbert A, Pierce RH, Greenberg PD, Hingorani SR. T-cell Localization, Activation, and Clonal Expansion in Human Pancreatic Ductal Adenocarcinoma. Cancer Immunol Res 2017;5(11):978–991. doi:10.1158/2326-6066.CIR-16-0322, PMID:29066497.
[74] Lu Y, Yuan X, Wang M, He Z, Li H, Wang J, *et al*. Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies. J Hematol Oncol 2022;15(1):47. doi:10.1186/s13045-022-01273-9, PMID:35488243.
[75] Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, *et al*. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018;359(6371):91–97. doi:10.1126/science.aan3706, PMID:29097494.
[76] Halsey TM, Thomas AS, Hayase T, Ma W, Abu-Sbeih H, Sun B, *et al*. Microbiome alteration via fecal microbiota transplantation is effective for refractory immune checkpoint inhibitor-induced colitis. Sci Transl Med 2023;15(700):eabq4006. doi:10.1126/scitranslmed.abq4006, PMID:37315113.
[77] Elkrief A, Waters NR, Smith N, Dai A, Slingerland J, Aleynick N, *et al*. Immune-Related Colitis Is Associated with Fecal Microbial Dysbiosis and Can Be Mitigated by Fecal Microbiota Transplantation. Cancer Immunol Res 2024;12(3):308–321. doi:10.1158/2326-6066.CIR-23-0498, PMID:38108398.
[78] Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, Katz L, *et al*. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science 2021;371(6529):602–609. doi:10.1126/science.abb5920, PMID:33303685.
[79] Park SR, Kim G, Kim Y, Cho B, Kim SY, Do EJ, *et al*. Fecal microbiota transplantation combined with anti-PD-1 inhibitor for unresectable or metastatic solid cancers refractory to anti-PD-1 inhibitor. J Clin Oncol 2023;41(Suppl 16):105. doi:10.1200/JCO.2023.41.16_suppl.105.
[80] Zhao W, Lei J, Ke S, Chen Y, Xiao J, Tang Z, *et al*. Fecal microbiota transplantation plus tislelizumab and fruquintinib in refractory microsatellite stable metastatic colorectal cancer: an open-label, single-arm, phase II trial (RENMIN-215). EClinicalMedicine 2023;66:102315. doi:10.1016/j.eclinm.2023.102315, PMID:38024475.
[81] Peng Z, Zhang X, Xie T, Shen L. Efficacy of fecal microbiota transplantation in patients with anti-PD-1-resistant/refractory gastrointestinal cancers. J Clin Oncol 2023;41(Suppl 4):389. doi:10.1200/JCO.2023.41.4_suppl.389.
[82] DeFilipp Z, Bloom PP, Torres Soto M, Mansour MK, Sater MRA, Huntley MH, *et al*. Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant. N Engl J Med 2019;381(21):2043–2050. doi:10.1056/NEJMoa1910437, PMID:31665575.
[83] Valles-Colomer M, Blanco-Míguez A, Manghi P, Asnicar F, Dubois L, Golzato D, *et al*. The person-to-person transmission landscape of the gut and oral microbiomes. Nature 2023;614(7946):125–135. doi:10.1038/s41586-022-05620-1, PMID:36653448.
[84] Sarkar A, McInroy CJA, Harty S, Raulo A, Ibata NGO, Valles-Colomer M, *et al*. Microbial transmission in the social microbiome and host health and disease. Cell 2024;187(1):17–43. doi:10.1016/j.cell.2023.12.014, PMID:38181740.
[85] Marcella C, Cui B, Kelly CR, Ianiro G, Cammarota G, Zhang F. Systematic review: the global incidence of faecal microbiota transplantation-related adverse events from 2000 to 2020. Aliment Pharmacol Ther 2021;53(1):33–42. doi:10.1111/apt.16148, PMID:33159374.
[86] Zhang S, Chen Q, Kelly CR, Kassam Z, Qin H, Li N, *et al*. Donor Screening for Fecal Microbiota Transplantation in China: Evaluation of 8483 Candidates. Gastroenterology 2022;162(3):966–968.e3. doi:10.1053/j.gastro.2021.11.004, PMID:34752816.
[87] He R, Li P, Wang J, Cui B, Zhang F, Zhao F. The interplay of gut microbiota between donors and recipients determines the efficacy of fecal microbiota transplantation. Gut Microbes 2022;14(1):2100197. doi:10.1080/19490976.2022.2100197, PMID:35854629.
[88] Smillie CS, Sauk J, Gevers D, Friedman J, Sung J, Youngster I, *et al*. Strain Tracking Reveals the Determinants of Bacterial Engraftment in the Human Gut Following Fecal Microbiota Transplantation. Cell Host

Microbe 2018;23(2):229–240.e5. doi:10.1016/j.chom.2018.01.003, PMID:29447696.
[89] Fischer M, Sipe BW, Rogers NA, Cook GK, Robb BW, Vuppalanchi R, *et al*. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated Clostridium difficile infection: description of a protocol with high success rate. Aliment Pharmacol Ther 2015;42(4):470–476. doi:10.1111/apt.13290, PMID:26096320.
[90] Song YN, Yang DY, Veldhuyzen van Zanten S, Wong K, McArthur E, Song CZ, *et al*. Fecal Microbiota Transplantation for Severe or Fulminant Clostridioides difficile Infection: Systematic Review and Meta-analysis. J Can Assoc Gastroenterol 2022;5(1):e1–e11. doi:10.1093/jcag/gwab023, PMID:35118227.
[91] Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, *et al*. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology 2015;149(1):102–109.e6. doi:10.1053/j.gastro.2015.04.001, PMID:25857665.
[92] Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, *et al*. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology 2015;149(1):110–118.e4. doi:10.1053/j.gastro.2015.03.045, PMID:25836986.
[93] Hui W, Li T, Liu W, Zhou C, Gao F. Fecal microbiota transplantation for treatment of recurrent C. difficile infection: An updated randomized controlled trial meta-analysis. PLoS One 2019;14(1):e0210016. doi:10.1371/journal.pone.0210016, PMID:30673716.