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Mini-review

Microbiota transplantation: Targeting cancer treatment

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ABSTRACT

Mounting evidence have demonstrated that gut microbiota plays a critical role in cancer patients' therapeutic responses to chemotherapy, radiotherapy and immunotherapy, including clinical efficacy and sensitivity to toxicity. These fascinating findings evoke a possibility of manipulating gut microbiota to optimize anti-cancer treatment from bench to beside. Microbiota transplantation (MT), including fecal microbiota transplantation (FMT) and selective microbiota transplantation (SMT), may improve the effect of anti-cancer treatment and/or reduce the related side effects. The safety and efficacy of MT in cancer treatment are the core of translational research in this promising field, which inspire us to focus on the MT technology and mechanism of MT targeting anti-cancer treatment. To perform clean FMT based on automatic methods by machine in exclusive laboratory has become true. Colonic transendoscopic enteral tubing as a novel delivering way for MT should bring convenience for frequent delivering in practice and feasible tool for confirming the therapeutic effect in research. The present review focuses on the recent findings on role of microbiota on chemotherapy, radiotherapy and immunotherapy, and the methodology, feasibility and challenges of MT in anti-cancer treatment.

1. Introduction

The human body harbors enormous microbiota that regulates physiological functions like host immunity, metabolism, cellular responses [1]. Gut microbiota changes its composition and function during the development of diseases, including cancers [2,3], inflammatory bowel disease (IBD) [4,5], hepatic disease [6–8], diabetes mellitus [9], nephropathy [10], microbiota-gut-brain disease [11]. In addition, increasing evidence demonstrated an interplay between gut microbiota and anti-cancer treatment (chemotherapy, immunotherapy and radiotherapy) [12,13]. Gut microbiota modulates the pharmacological action of drugs during chemotherapy through multiple mechanisms like translocation, metabolic regulation, immunomodulation [14–16]. The gradual alteration of intestinal microbiota plays vital role in the development of radiotherapy related side effects [12]. Furthermore, the host response to anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or programmed death protein 1 (PD-1)/programmed death protein 1 ligand (PD-L1) immunotherapy can be regulated by gut microbiota [17,18]. Therefore, reestablishing gut microbiota may fortify the host's anti-cancer defense and reduce the therapy-related toxicity.

The fecal microbiota from a healthy donor into the intestine of a patient to remodel gut microbiota was coined fecal microbiota transplantation (FMT), which is a strategy originating from traditional Chinese medicine at least 1,700 years ago [19]. Accumulating evidences have shown a potential role of microbiota in extra-intestinal sites, such as vagina [20], sinus [21] and skin [22]. However, it is not easy for patients to accept the microbiota transplantation into organs beyond gastrointestinal tract. Therefore, a strategy called selective microbiota transplantation (SMT) was proposed to understand the concept of microbiota transplantation (MT). Then, MT includes the whole profile of microbiota transplantation (e.g., FMT and vaginal microbiota transplantation) and the SMT for stimulating of the whole profile of microbiota (e.g., the intermediate composition of bacteria between traditional probiotics and whole profile of microbiota) [23]. So far, FMT-guided cancer treatment has displayed their potential in improving anti-cancer responses and/or reducing related adverse events [17,24,25]. Similarly, the discovery of specific strains involved in the performance of anti-cancer treatment of diverse tumors has also boosted the development of SMT. In consequence, MT may emerge as an effective aid to anti-cancer treatment in the future.

This mini-review focuses on the status of gut microbiota in oncotherapy, including chemotherapy, radiotherapy and immunotherapy, and the efficacy and challenges of MT in anti-cancer treatment.

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Abbreviations

IBD	Inflammatory bowel disease
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
PD-1	Programmed death protein 1
PD-L1	Programmed death protein 1 ligand
FMT	Fecal microbiota transplantation
SMT	Selective microbiota transplantation
MT	Microbiota transplantation
CTX	Cyclophosphamide
GF	Germ-free
TLR4	Toll-like receptor 4
MYD88	Myeloid differentiation primary response 88
CPT-11	Irinotecan
CIPN	Chemotherapy-induced peripheral neuropathy
TLR2	Toll-like receptor 2
COX-2	Cyclooxygenase-2
ICI	Immune checkpoint inhibitors
mAb	Monoclonal antibody
CDI	*Clostridium difficile* infection
UC	Ulcerative colitis
GMP	Good Manufacture Practice
TET	Transendoscopic enteral tubing

2. Gut microbiota regulates the efficacy and toxicity of chemotherapy

Chemotherapy is a widely used and most preferred cancer treatment [26]. However, it comes with sizeable treatment-related morbidity and mortality [27]. Preclinical studies have revealed that gut microbiota shows an intimacy with the anti-cancer effect and toxicity of chemotherapeutic drugs [28].

Recent researches have demonstrated the regulatory role of gut microbiota in local immune responses during chemotherapy [14,25]. The gut microbiota always works with cyclophosphamide (CTX) to stimulate anti-tumor immune responses. Using mice models, Viaud and his colleagues [15] demonstrated that CTX led to the discontinuities of intestinal barrier and subsequently propelled the selective translocation of specific Gram-positive bacterial species (mainly *Lactobacillus johnsonii* and *Enterococcus hirae*) into secondary lymphoid organs. These translocated bacteria boosted anti-cancer adaptive immune responses of “pathogenic” T helper 17 cells and memory TH1 cells [14,15,25]. Interestingly, Daillere et al. [14] also found that a Gram-negative bacterium (*Barnesiella intestinihominis*), which can enhance systemic polyfunctional TC1 and TH1 cell responses and restore the ability of intratumoral δγ T cells producing IFN-γ, endowed CTX with a stronger immunological effect on cancer. No matter broad spectrum antibiotics, vancomycin or colistin all compromised the full-blown anti-cancer activity of CTX in tumor-bearing mice [14]. Similarly, the platinum chemotherapeutic agents exert tumor-braking effects in a microbiologically dependent manner [29]. The antineoplastic effect of oxaliplatin or cisplatin on subcutaneous transplantable tumors is dramatically attenuated in microbiota¬depleted mice and in germ¬free (GF) mice, a result of decreased reactive oxygen species and diminished intratumoral DNA damage [30]. Moreover, Gui et al. reported that the antigrowth and proapoptotic effects of cisplatin were reinstated when antibiotic¬treated mice were fed with the probiotic *Lactobacillus acidophilus* [31]. In contrast, some microbial bacteria promote the development of chemoresistance. High-level *Fusobacterium nucleatum* increased colorectal cancer recurrence and was an independent predictor of colorectal cancer aggressiveness [13]. Further investigation evidenced that *F. nucleatum* targeted Toll-like receptor 4 (TLR4) and myeloid differentiation primary response 88 (MYD88) signaling pathway, induced a loss of specific micro RNAs, activated autophagy pathway, and ultimately strengthened colorectal cancer resistance to Oxaliplatin and fluorouracil [13].

Chemotherapy-induced side reactions, such as severe intestinal toxicity and peripheral neuropathy, challenge the deciding of drug dose [32,33]. Mechanistic evidence have unveiled a dual role of intestinal bacteria in the process of chemotherapeutic-induced mucositis. Some commensal bacteria produced beneficial metabolites, such as butyrate, which could reduce the toxicity of chemotherapeutic drugs [34]. Inversely, *β-glucuronidase*-producing bacteria dissociated SN-38G into toxic SN-38 in the gastrointestinal tract, a process leading to irinotecan (CPT-11)-associated intestinal damage [16,35,36]. GF mice mono-associated with TG1 strain (*Escherichia coli* strain producing *β-glucuronidase*) demonstrated an increase in intestinal permeability compared to the GF mice mono-associated with L91 strain (a mutant *E. coli* strain that can't produce *β-glucuronidase*) [36]. This conclusion has been confirmed by other experiments in which mice treated with CPT-11 and *β-glucuronidase* inhibitors were protected away from CPT-11-induced diarrhea [37]. Chemotherapy-induced peripheral neuropathy (CIPN) is often characterized by devastating neuropathic pain that lasts from months to years, leading to dose-limiting and impaired anticancer effect [38]. Shen et al. [33] reported that when GF status was reversed by gavage of feces from specific pathogen-free mice donors, protection that obstructed progression of mechanical hyperalgesia was abrogate. Moreover, evidence indicated that Lipopolysaccharides-TLR4 pathway was involved in the development of mechanical hyperalgesia during oxaliplatin therapy [33]. Oxaliplatin-associated mechanical hyperalgesia was milder in TLR4 knockout (TLR4 $-/-$) mice than in littermate heterozygous (TLR4 $+/-$) mice, which agreed with other findings on chemotherapy-induced peripheral neuropathy models [39].

3. Interaction between radiotherapy and gut microbiota

The effectiveness of radiotherapy in the curative and palliative treatment of cancer has been well demonstrated. However, radiation exposure also damages the surrounding healthy tissues, and especially rapid proliferating tissues including epithelia and bone marrow [40,41]. Radiotherapy induces death of the intestinal crypts, breach of the mucosal barrier, and changes in the microbiota composition, further triggering inflammation and immune response [42,43]. Emerging evidence indicated a pivotal role of the gut microbiota in radiation-induced bowel injury which perplexed cancer patients receiving radiation to their abdominopelvic region and manifested as diarrhea, abdominal pain, hematochezia, strictures, and bowel obstruction, abscess formation, malabsorption and other symptoms [44]. Several studies demonstrated that radiation to cancer patients resulted in significant alterations in the microbiota profile [12,24,45,46]. Besides, radiation-induced dysbiosis in turn triggered radiation-related disease, including mucositis, diarrhea and fatigue in cancer patients [12,47], which lowered patients’ life quality and even led to the suspension of treatment. Co-incubating fecal bacterial suspensions from irradiated mice increased the level of TNF-α and IL-1β secreted by the epithelial cells compared with naïve mice. Furthermore, GF mice inoculated with radiation-induced microbiota showed severer radiation damage compared to GF mice inoculated naïve microbiota [12]. Given that the gut microbiota of radiated mice showed strong pathogenic power in tissue damage both in vitro and in vivo, Gerassy-Vainberg et al. [12] concluded that localized dysbiosis was a process involved in radiation-induced damage. They also first displayed the role of post-radiation microbiota in the induction of IL-1β secretion. Radiotherapy-disrupted intestinal microbiota made mice more vulnerable to radiation damage by facilitating the secretion of IL-1β. IL-1β may exacerbated mucositis through breaking tight junction and promoting inflammatory process

Table 1
Gut microbiota associated with cancer treatment.

Cancer treatment	Favorable (F) or unfavorable (UF) bacterium	Related mechanism	Outcome	Animal (A) or human (H) study
Chemotherapy	*Enterococcus hirae* (F) *Lactobacillus johnsonii* (F) [14]	The selective translocation of *E.hirae* and *Lactobacillus johnsonii* induced systemic pTH17 cell immune response, increased intratumoral CTL/Treg ratio	Reinstated anticancer effect of CTX	A&H
	Barnesiella, intestinihominis (F) [14]	*B.intestinihominis* markedly facilitated the abundance of polyfunctional Tc1 and Th1 cell, increased the infiltration of IFN-γ-producing δγ T cells	Ameliorated anticancer effect of CTX	A&H
	Lactobacillus acidophilus (F) [31]	*Lactobacillus acidophilus* up-regulated the tumor suppressor gene CDKN1B and IFN-γ, GZMB, PRF1 mRNA expression, down-regulated the tumor oncogene VEGFA	Enhanced the antigrowth and proapoptotic effects of cisplatin	A
	Fusobacterium nucleatum (UF) [13]	*F. nucleatum* targeted TLR4 and MYD88 signaling pathway, induced a loss of miR18a* and miR4802, and subsequently up-regulated the expression of autophagy elements ULK1 and ATG7	Promoted colorectal cancer resistance to Oxaliplatin and 5-FU	A&H
	β-glucuronidase producing bacteria (UF) [36]	Microbial *β-glucuronidase* hydrolyzed part of the glucuronic acid, concurrently released the toxic form SN-38 metabolite into the intestine, increased intestinal permeability and inflammatory parameters	Aggravated the intestinal lesions caused by CPT-11	A
	Related Gram-negative bacterium (UF) [33]	The Gram negative bacterium wall component LPS, a ligand of TLR4, enabled and promoted macrophages to secret inflammatory cytokines (ie. IL-6 and TNFα)	Promoted the development of mechanical hyperalgesia induced by oxaliplatin	A
Radiotherapy	*Bacteroidetes* (UF) *Proteobacteria* (UF) *Firmicutes* (F) etc. [12]	Radiotherapy induced localized dysbiosis, while altered gut microbiota triggered an specific IL-1β secretion and other mucosal cytokines release reversely	Exacerbated radiation-induced intestinal damage and transmitted susceptibility to colitis	A
	Lactobacillus rhamnosus GG (F) [50]	A TLR2/MyD88 signalling mechanism leading to repositioning of constitutive COX-2-expressing mesenchymal stem cells to the crypt base was invoked with the intervention of *Lactobacillus rhamnosus* GG.	Reduced radiation-induced epithelial injury and improved crypt survival	A
Immunotherapy	*Akkermansia muciniphila* (F) [17]	*A.muciniphila* increased the accumulation of $CCR9^+CXCR3^+CD4^+$ T cells in tumor beds, induced the secretion of interleukin-12 and up-regulated PD-L1	Restored the compromised efficacy of PD-1 blockade in antibiotic-treated mice and in GF mice with FMT from non-responder feces	A&H
	Faecalibacterium genus (F) [52]	Patients/mice with high abundance of *Faecalibacterium genus* had strengthened antigen presentation capacity, higher levels of effector T cell ($CD45^+CD11b^+Ly\text{-}6G^+$) and a preserved cytokine immune response	Improved antitumor immune response of PD-1blockade	A&H
	Bacteroidales (UF) [52]	Patients/mice with high abundance of *Bacteroidales* demonstrated a higher levels of regulatory $CD4^+Foxp3^+$ T cells and a blunted cytokine response	Impaired antitumor immune response of PD-1blockade	A&H
	Bifidobacterium longum (F), *Lactobacillus spp* (F), *Enterococcus faecium* (F); *Ruminococcusobeum* (UF), *Roseburiaintestinali* (UF) etc. [57]	Patients/mice with "favorable" gut microbiota showed a significant increased Batf3-lineage dendritic cells, augmented Th1 responses and decreased $Foxp3^+CD4^+$ regulatory T cells	Improved the tumor control effectiveness of anti-PD-L1 immunotherapy	A&H
	Bacteroides. thetaiotaomicron (F) *Bacteroides. fragilis* (F) *Burkholderia cepacia* (F) [60]	The composition of gut microbiota mobilized $CD11b^+$ dendritic cells and then mounted interleukin-12-dependent Th1 anti-tumor immune responses	Boosted tumor control while reducing histopathological signs of colitis induce by anti-CTLA-4 therapy	A&H
	Bifidobacterium (F) [63]	The influence of *Bifidobacterium* in alleviating gut immunopathology may be depend on regulatory T cells.	Mitigated intestinal toxicity induced by CTLA-4 blockade without affecting its antitumor activity	A

pTH17 cell: pathogenic T helper 17 cell; CTL: cytotoxic lymphocyte; Treg: T regulatory cell; CTX: cyclophosphamide; IFN-γ:interferon-γ; CDKN1B: cyclin dependent kinase inhibitor 1B; GZMB: granzyme B; PRF1: perforin-1; VEGFA: vascular endothelial growth factor A; TLR4: Toll-like receptor 4; MYD88: myeloid differentiation primary response 88; 5-FU: fluorouracil; CPT-11: irinotecan; GF: germ-free; LPS: lipopolysaccharides; TLR2: Toll-like receptor 2; COX-2: Cyclooxygenase-2; PD-L1: programmed death protein 1 ligand; PD-1: programmed death protein 1; FMT: fecal microbiota transplantation; CTLA-4: cytotoxic T-lymphocyte–associated protein 4.

[48]. Encouragingly, a meta-analysis compiling six independent randomized control studies proved the radioprotection of probiotics, where *Lactobacillus* were all contained in the composition of probiotics [49]. The mechanism by which *Lactobacillus* exerted beneficial effect may through a Toll-like receptor 2 (TLR2) and MyD88-dependent signaling pathway resulting in repositioning of cyclooxygenase-2 (COX-2) - expressing mesenchymal stem cells to the crypt region and further improving crypt survival and reducing the epithelial injury in the mouse intestine [50].

4. Gut microbiota affects the outcome of immunotherapy

Administrating immune checkpoint inhibitors (ICI) targeting PD-1, PD-L1 and CTLA-4 unleashes T lymphocyte-mediated adaptive immune response [29,51], a strong anticancer activity detected in experimental clinical studies recently [17,52–54]. The composition of a patient's intestinal microbiota has been shown as an important factor in modulating the host response to anti-PD-1/PD-L1 or anti-CTLA-4 immunotherapy [53–56].

Anti¬PD-1/PD-L1 immunotherapy is highly effective to treat melanoma, renal cell carcinoma, non-small-cell lung cancer and others [17,52,57]. Routy et al. [17] observed that antibiotic treatment, performed within 2 months before or 1 month after PD-1/PD-L1 monoclonal antibody (mAb) treatment, shortened the progression-free survival and overall survival of patients. This finding is contrast to that conducted by Pushalkar who found that the combination of PD-1 blockade and antibiotics showed synergistic anti-pancreatic cancer effect through inducing T-cell activation [58]. This contrary indicates that different cancer types may change microbial components in different manners, thus enhancing or weakening the function of ICI [59]. In Routy's research, *Akkermansia muciniphila* supplement restored the impaired efficacy of PD-1 blockade in mice with FMT from non-responder [17]. Two additional studies also identified a correlation between microbial status and treatment responsiveness [52,57]. Gopalakrishnan et al. [52] discovered the significantly elevated abundance of *Faecalibacterium genus* in responding patients and *Bacteroidales* in non-responders. This is in accordance with a published article reporting that patients on CTLA-4 blockade with a higher abundance of *Faecalibacterium* in the gastrointestinal tract had a prolonged progression-free survival compared to those with a higher abundance of *Bacteroidales* [18]. Some studies have also proved that the presence of *Bifidobacterium longum* could ameliorate the outcome of anti-PD-L1 therapy [54,57]. The reasons why the microbiota differs from individuals (responder vs non-responder) in similar experiments may reside in bacterial taxa, cancer type, metagenomics technologies, environment factors and others [53]. Irrespective of the above differences, all three studies highlighted the immunostimulatory role of gut microbiota in advanced cancer patients receiving anti-PD-1 therapy [17,52,57]. These experimental results suggest that manipulating the gut microbiota may prevent primary resistance to ICIs and further improve the effectiveness of immunotherapy.

Studies also supported the potential role of gut microbiota in mediating the efficacy of CTLA-4 blockade immunotherapy. A report from Vetizou et al. [60] validated that the anti-cancer effects and related side effects of ipilimumab, a mAb against CTLA-4 directly, were closely associated with intestinal *Bacteroides spp*. Anti-CTLA-4 immunotherapy failed to decrease tumor burden in GF mice. However, oral gavage with *B. thetaiotaomicron*, *B. fragilis* or *Burkholderiacepacia* reestablished antineoplastic responses of ipilimumab in GF mice by triggering the maturation of intratumoral dendritic cells and inducing IL-12-dependent TH1 response in tumor-draining lymph nodes [60]. Regrettably, the therapeutic response of anti-CTLA-4 usually accompanies with immune-related adverse events, mostly colitis that appears in other ICIs [61,62]. But a cocktail of *Burkholderiacepacia* and *B. fragilis* could improve the extent of intestinal injury and colitis [60]. Given that *Burkholderiacepacia* and *B. fragilis* can initiate favorable anti-tumor response, the selective transplantation of *Burkholderiacepacia* and *B. fragilis* into intestinal may support CTLA-4 mAb therapy through enhancing tumor control while reducing intestinal toxicity. In addition, Wang and his colleagues also discovered that a commonly probiotic *Bifidobacterium* could ameliorate gut immunopathology depending on regulatory T cells without impairing the therapeutic efficacy [63]. This provides a new horizon to explore the role of *Bifidobacterium* that has already demonstrated beneficial influence on anti-PD-L1 therapy [54,57], in the combination of anti-PD-1 and CTLA-4 tumor immunotherapy.

5. Optimizing cancer treatment via microbiota transplantation

The notion of applying the microbial components or their products in anti-cancer treatment is not new. Coley used the mixed toxins from *Bacillus prodigiosus* and *Streptococcus* erysipelas to treat sarcoma in 1891 [64], *Mycobacteria* are still being used for the bladder cancer therapy [65]. There are three main strategies of gut microbiota intervention in tumor therapy: dietary intervention [66,67], probiotics supplementation [68,69] and MT [17,24,25].

FMT has shown its therapeutic role in recurrent *Clostridium Difficile* infection (CDI), IBD, epilepsy, autism, hepatic disease, metabolic syndrome, and others [70–76]. Recently, the first case series of two patients who suffered refractory ICI-associated colitis achieved complete remission of symptoms following FMT was reported, with reconstitution of gut microbiota and changes in T cell composition within the colonic mucosa [77]. In spite of few clinical application of FMT in tumor therapy, animal model experiments have revealed the potential of FMT in the anti-cancer treatment [17,24,25]. FMT can enhance anticancer effects, which has been shown in three recent reports where the response of antibiotic-treated mice or GF mice to anti-PD-1 therapy was reinforced when they receive feces from responsive patients [17,52,57]. On the other hand, multiple FMTs could restore the irradiation-impaired gut microbial composition, improve gastrointestinal tract function and epithelial integrity without accelerating tumor growth, suggesting the protection role in reducing radiotherapy-associated side effects [24].

The association between specific probiotic strains and anti-cancer treatment efficacy (including those mentioned in Table 1) lays a theoretical foundation for the development of SMT. For example, an oral gavage with a mixture of Gram-positive bacteria (*L. johnsonii* + *E. hirae*) in antibiotics-treated specific pathogen-free mice improved antineoplastic activity [25]. And DSF extract, a high concentration of probiotic formulation containing *Bifidobacterium, Lactobacillus and Streptococcus spp* [78], could counteract Paclitaxel-induced neuropathic pain, bringing no toxicity in the long-term use of therapies [79]. The addition of DSF efficiently counteracted the Paclitaxel-induced increase of pro-inflammatory and chemokines including p-STAT3, PI3K, p-FAK, p-JAK2 and IL-8, which are potential triggers of the nociceptive process in CIPN. A first-ever clinical trial has been conducted by our team to investigate the efficacy of SMT in the treatment of patients who have been endoscopically proven radiation enteritis (NCT03516461). Given the selectivity of SMT in gut, certain drawbacks of traditional FMTs may not appear [29]. However, SMT in gut might be less effective than FMT for serious diseases. The mechanism between specific strains of bacteria and anti-cancer treatment need further exploration.

A recent pilot study [80,81] demonstrated that 57.3% of ulcerative colitis (UC) patients under steroids-dependent status achieved clinical improvement and steroids-free remission after using single FMT, multiple FMTs or FMT plus steroids. Then this strategy coined as “step-up FMT” proposed by Zhang et al. [80,82], involves three steps: step 1, single FMT; step 2, multiple FMTs; step 3, combination of FMT and traditional medications, which is effective for steroid-dependent UC [80], severe or complicated CDI [83] and cancers [17,52,57], especially when patients do not respond to regular medications. In addition, some clinical trials have been launched to explore the efficacy of step-up FMT

in patients with melanoma or genitourinary cancer (NCT03353402, NCT03819296, NCT03341143). In the new era of using selected microbiota for transplantation, the strategy of using SMT for cancer treatment should be same as step-up FMT [23]. The step-up MT strategy as a promising application in treatment-naïve patients, and treatment-experienced patients who responded poorly or suffered severe side effects was shown in Fig. 1.

6. Issues of fecal microbiota transplantation in practice

The use of FMT is limited by its methodology, potential adverse events, the insufficient clinical evidence and the ethical issues in current stage. There have been a variety of reported adverse events, including infection, aspiration and even death [23]. Standardized, humanized strict laboratory procedures and clinical work flow are key to guarantee the quality of microbiota, the efficacy of FMT, and control the potential risks [23]. Therefore, before becoming a mainstream treatment, FMT should be standardized in the future.

We aimed to perform “clean” FMT for patients since 2012. The specially designed machine (GenFMTer, FMT Medical, Nanjing, China) for automatic purification of microbiota from stool makes the process in lab quality controllable and easier than manual method. As a center bank for providing FMT service in China, we established the laboratory for fecal bacteria preparation matching Good Manufacture Practice (GMP) level. The “one-hour FMT protocol”, which means the preparation time “from defecation to infusion or to freezing” is within one hour with the help of auto-purification system GenFMTer [82], significantly different from “six-hour FMT protocol” mainly used in America and Europe, can better protect microbiota function and improve clinical efficacy [71].

Proper delivering way for FMT according to individual condition can satisfy patients and reduce side effects [84,85]. Microbiota can be delivered through upper-gut, mid -gut and lower-gut [84]. The upper-gut delivery refers to oral intake of fecal microbiota suspension or capsules [23,86]. In mid-gut delivery, the microbiota suspension is delivered into the small intestine (beyond the descending duodenum) through endoscopy, nasoduodenal tube, nasojejunal tube, small intestine stoma, percutaneous endoscopic gastrojejunostomy [84] and mid-gut transendoscopic enteral tubing (TET) [85]. Colonoscopy, distal ileum stoma, enema, colostomy and colonic TET [84] can be used in lower-gut delivery. The latest progress on MT delivering is colonic TET, as the most logistic delivering way for microbiota to colon. Colonic TET is convenient, time-saving, safe and suitable for frequent FMTs and colonic medication administration [84,85].

The strict donor screening is another issue to make FMT safe and effective. The strategy of screening healthy donor is to use exclusive methods in eight dimensions: age, physiology, pathology, psychology, veracity, time, living environment and recipients [87,88]. The long-term safety of FMT and SMT needs long-term follow-up. More than ten years of follow-up was required by American Gastroenterological Association [89] and China Microbiota Transplantation System [23], though our recent pooled studies showed no adverse events in 139 CD patients [87] and only one serious adverse event in 109 UC patients during 1–5 years follow-up [88]. The cut-point for clarifying the short-term and long-term FMT-related adverse events is one month post-FMT in these studies.

7. Conclusion

In recent years, exploiting gut microbiota to assist anti-cancer treatment has aroused the interest of researchers. Patients’ responses to anti-cancer treatment and sensitivity to adverse events can be modulated by gut microbiota. The gut microbiota can improve or impair the pharmacological effects of chemotherapy drugs, thus changing the therapeutic response and related adverse events. The radiotherapy-related toxicity often accompanies with structured microbial community in tumor patients. Similarly, the abundance of specific gut microbiota has a vital impact on the host response to anti-PD-1 and anti-CTLA-4 immunotherapy. Experimental animal models have shown FMT and SMT before anti-cancer treatment can reconstruct the gut microbiota and improve the immune status of host, and further enhance the effectiveness of oncotherapy or reduce tumor resistance as well as relevant adverse events, suggesting the promising future of step-up MT in cancer treatment. To guarantee the safety and efficacy of MT in cancer treatment in this promising field, the MT technology and mechanism of MT targeting anti-cancer treatment cannot be neglected. Performing clean FMT based on automatic methods by machine has been used in clinical practice. Colonic TET as a novel delivering way for FMT or SMT should bring more convenience for frequent delivering in practice and more effectiveness for confirming the possible therapeutic value in patients. More attractive studies from translational researches on microbiota will be reported in the coming years in cancer treatment.

Author contributions

All authors were involved in the conception, preparation of the manuscript, and the final version of the manuscript has been read and approved by all the authors before its submission.

Conflicts of interest

Faming Zhang invented the concept of GenFMTer and transendoscopic enteral tubing and devices related to it. Xia Wu, Ting Zhang, Xiong Chen, Guozhong Ji declare that they have no competing interests to declare.

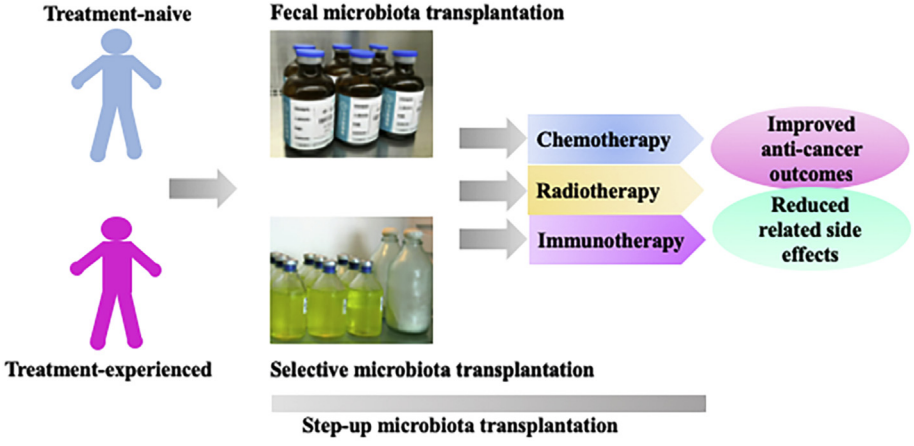

Fig. 1. Application strategy of MT in cancer treatment. The application of MT in cancer treatment can be classified into two categories: Firstly, for treatment-naive patients who are newly diagnosed with tumors, reconstruction of gut microbiota by transplanting related “favorable” bacterium (the step 1 and step 2 of step-up MT) may promote the anti-tumor effect and/or reduce the occurrence of related toxic events of step 3 (combination MT with chemotherapy, radiotherapy or immunotherapy); Secondly, the microbial environment of treatment-experienced patients who suffered dissatisfied response or severe side effects can be improved through step-up MT strategy so as to stimulate the host antineoplastic activity and/or reduce the intestinal toxicity, pain and other side effects.

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