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Review Article

An Insight into the Clinical Application of Gut Microbiota during Anticancer Therapy

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The gut microbiota, regarded as "the second genome" of human, is responsible for a considerable number of key physiological responses in the host, including the regulation of host immunity, the prevention of pathogen infection, the synthesis and metabolism of critical molecules, and others. More importantly, recent research highlighted that it could also play an indispensable role during anticancer therapy. By interacting with the host immunity or producing direct modifications on the drugs, the gut microbiota can ultimately contribute to the effectiveness of anticancer treatments and also overcome the therapy-induced adverse effects. In this review, we discuss the potential mechanisms of gut microbiota in facilitating anticancer therapy and illustrate the applications of different commensal bacterial species in preclinical and clinical trials, which may provide insights into how the gut microbiota could be used as a promising adjuvant therapy option for the future treatment.

1. Introduction

In the course of modern medical research, a considerable number of diseases previously known as noncurable have been overcome, yet cancer being the most significant cause of mortality remains a challenge for both medical research and the modern society. The fight of human against cancer is a long and tough journey with several milestones in the therapeutic methods, which include surgery, chemotherapy, radiotherapy, and the recent emergence of immunotherapy. These options have contributed greatly to the overall survival of cancer patients. A statistic shows that by the time of 2019, the number of patients with a cancer history has exceeded 16.9 million in the United States, and this number is predicted to reach 22.1 million by the time of 2030 [1]. To date, based on the mechanisms of tumorigenesis and progression, the treatments for cancer have become increasingly sophisticated and standardized, while some side effects are still inevitable. Statistical studies have shown that 64.2% of melanoma patients treated with ipilimumab experienced immune-related side effects in Phase I to Phase III clinical studies, with the symptoms of fever, abdominal pain, and vomiting, which may even progress into intestinal perforation [2, 3]. The chance of developing cardiovascular disease (CVD) after radiotherapy or chemotherapy is also high, especially in patients with breast cancer and hematological malignancies [4]. In addition, the anticancer therapy can also cause disturbance in gut microbiota balance and further impair health conditions. For example, clinical evidence has shown that chemotherapy could lead to a reduction in the number of *Lactobacillus* and *Bifidobacterium*, as well as an increased *Escherichia coli* (*E. coli*) and *Staphylococcus*. This could further contribute to enhanced inflammatory response and damaged barrier function. Similarly, after radiotherapy, the diversity of gut microbiota is also impaired, with increased risk for several diseases such as inflammatory bowel disease (IBD) and type 2 diabetes (T2D) afterwards. Other limitations of anticancer therapy include systemic toxicities, adaptive drug resistance, and different response rate among patients, which require further investigations

on searching for an appropriate adjuvant therapy to ameliorate the adverse effects and hopefully improve the therapeutic efficacy.

Based on the development of high-throughput sequencing technology, one of the best choices to fill in this gap emerges as the study on the gut microbiota. Regarded as "the second genome" of human, the gut microbiota houses a wealth of microbial cells, genomic DNA, and metabolites, with the number considered to reach several trillions [5, 6]. The microorganisms that coexist with host in the epithelium of gut lumen, also known as commensal bacteria, actively participate in the homeostasis of human body by harnessing the balance of physiological and pathological conditions of the host. According to the previous research, this property of gut microbiota is mainly achieved by involving in several key functions of the host, including but not restricted to the regulation of host immunity, the prevention of pathogen infection, and the synthesis and metabolism of critical molecules [5]. As a result, a hypothesis is that these properties of gut microbiota may also be exploited in the treatment of many chronic diseases, especially cancer.

Fortunately, many studies so far have evidenced this hypothesis, with several research papers indicating different microbiota strains could exert different functions and that modulating the composition of gut microbiota could facilitate the anticancer treatment. This points to the potential role of gut microbiota as a promising adjuvant therapy for cancer and definitely paved the way to a new stage of cancer therapy. This review focuses on exploring the regulating role of the gut microbiota in several therapeutic methods for cancer and discusses how different manipulation strategies could affect the efficacy of the treatment.

2. The Underlying Mechanisms: How Does the Gut Microbiota Work in Anticancer Therapy

A framework of the interactions between gut microbiota and the host is first brought up in details by Alexander et al. describing a "TIMER" framework which includes translocation, immunomodulation, metabolism, enzymatic degradation, and reduced diversity [7]. It is believed that the gut microbiota is able to serve as an antitumoral agent through their unique properties, including secretion of toxic substances, competition for nutrients, and harnessing the immune responses of the host [7]. Nevertheless, the recent research showed that the gut microbiota-host interaction seems to be more complex. Here, we mainly focus on the influence of gut microbiota on the treatment and how they are able to facilitate the efficacy of these therapeutic strategies (Figure 1).

2.1. Eliciting the Functions of Host Immune System. The immunological effects of gut microbiota have been well-recognized. Evidence has proposed that in the physiological conditions, the commensal gut microbiota is able to form a "barrier" against pathogenic invasion and thus responsible for the maintenance of a healthy local gut immunity. On the other hand, the disruption of this barrier, therefore, would lead to a large spectrum of pathological conditions such as diabetes, gastrointestinal disease, and oncogenesis [8, 9].

As a result, these findings have led to numerous research studies exploring the interaction between gut microbiota and host immune system, especially during anticancer therapy. One of the important properties of gut microbiota is that it could alter the efficacy of chemotherapeutic drugs by stimulating the immune responses of the host. As Daillère et al. reported, the chemotherapy agent cyclophosphamide (CTX) exerts its therapeutic effect with the aid of two bacterial species, *Enterococcus hirae* and *Barnesiella intestinihominis* [10]. Upon administration, cyclophosphamide could induce the translocation of *E. hirae* to the secondary lymphoid organs, as well as the accumulation of *B. intestinihominis* in the colon. This further contribute to the activation of immune responses and the recruitment of several immune effector cells, including the increase of $CD8^+$ T cells, the restoration of IFN-γ-producing $\gamma\delta$T cells infiltrating in the tumor sites, and the reduction of regulatory T cells (Tregs) [10]. Altogether, these immune responses help to boost the therapeutic effects of cyclophosphamide, leading to a better clinical outcome of patients. Similarly, the *Bifidobacterium* species could also strengthen the immunity of the host through orchestrating the production of anticancer T cells, demonstrated by increased infiltrating $CD8^+$ T cells stimulated around the tumor site in a melanoma model [11].

Aside from the recruitment of immune effector cells, the gut microbiota also has the ability to generate an inflammatory state which is required for the antitumor response. Previous literatures support the function of *Alistipes* in stimulating the tumor necrosis factor (TNF) production through the activation of Toll-like receptor 4 (TLR-4), mainly by priming the tumor-associated myeloid cells [12, 13]. By providing oral administration of the bacteria *Alistipes shahii* to mice previously treated with antibiotics, the ability of tumor-associated myeloid cells to produce TNF is reinstated, together with an amelioration of the antitumoral response [13]. Overall, these findings suggest that the gut microbiota could contribute to an efficient antitumor response via stimulating the immune response both locally and systemically.

2.2. Production of ROS. The reactive oxygen species (ROS) is a highly reactive substance with the ability to facilitate cell apoptosis via causing genotoxicity and persistent cell cycle arrest. It is generated during cellular metabolism as a normal metabolite and, more importantly, produced in response to application of several chemotherapeutic drugs such as platinum compounds and alkylating agents [13, 14]. Oxaliplatin, a platinum compound, is believed to utilize ROS to achieve antitumor response. Previous research highlights its therapeutic effect that could be regulated through the gut microbiota, manifested with an increased myeloid-cell ROS production and survival in the presence of gut microbiota and reduced tumor remission after ABX treatment or in germ-free mouse model. Therefore, it is suggested that by modulating the composition of gut microbiota, ABX could be used to fine-tune the therapeutic effect of ROS-generating cytotoxic drugs, keeping a balance between the

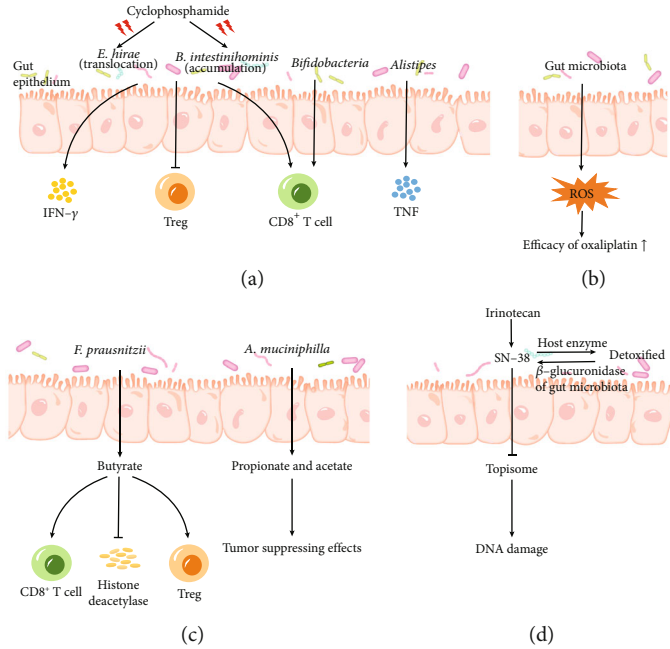

Figure 1: Potential mechanisms of gut microbiota in facilitating anticancer therapy. (a) The gut microbiota is proved to exert its function by eliciting the host immune responses. *E. hirae* translocation and *B. intestinihominis* accumulation induced by cyclophosphamide treatment could increase IFN-$\gamma$and $CD8^+$ T cells and, at the same time, reduce the amount of Tregs. *Bifidobacterium* is able to increase infiltrating $CD8^+$ T cells. *Alistipes* generates an inflammation state for antitumoral response by stimulating the production of TNF. (b) Gut microbiota is able to facilitate ROS production, which is responsible for enhanced drug efficacy. (c) The anti-inflammatory microbial metabolites produced by gut microbiota contribute to the enhancement of antitumor immunity. *F. prausnitzii* produces butyrate to stimulate the differentiation and accumulation of Tregs, the activation of $CD8^+$ T cells, and the inhibition of histone deacetylase. *A. muciniphila* produces propionate and acetate with tumor suppressing property. (d) Gut microbiota directly acts on drug biotransformation. The bacterial β-glucuronidase increases SN-38, the active and toxic form of irinotecan, and thus contributes to increased intestinal adverse effects.

cytotoxic effect to tumor cells and damage to bystander tissues [13].

2.3. Production of Anti-inflammatory Microbial Metabolites. Serving as an indispensable part in the metabolic activity in the human body, the commensal microbiota contributes to the production of approximately 50% of metabolites in the plasma [15, 16]. Among all the microbiota involved, the short-chain fatty acid- (SCFA-) producing microbiota specifically facilitate the enhancement of antitumor immunity [17]. It has been well-documented that *Faecalibacterium prausnitzii*, a microbiota known to produce butyrate, could act as a protective regulator of colorectal cancer [15]. The underlying mechanism depends on the anti-inflammatory property of butyrate, with evidence demonstrating that the butyrate contributes to the differentiation and accumulation of Tregs. Other important functions of butyrate, according to previous research findings, include its inhibitory effect on the histone deacetylase, and thus further impair the transcription and translation of oncogenic genes [12] and the stimulation on $CD8^+$ T cells for releasing effector molecules [18]. Indeed, the number of butyrate-producing bacteria in CRC patients is significantly lower compared with that in the healthy cohort, and the tumor size in CRC patients also showed a negative correlation with fecal butyrate levels [19]. In line with the antitumoral effects of butyrate, previous studies have pointed out the relation between dietary fibers and the attenuation of CRC [20], and Hu et al. showed that by providing resistant starch to the mouse model favors the colonization of bacteria that could produce butyrate with a decreased level of colitis-associated colorectal cancer [19].

Besides *Faecalibacterium prausnitzii*, bacteria *Akkermansia muciniphila* is also shown to be a critical source of SCFA, producing propionate and acetate as part of the tumor suppressing property of commensal microbiota. These evidences have pointed to the feasibility of manipulating fecal microbiota with dietary components to control cancer progression and achieve a better clinical outcome.

2.4. Modifications on the Drug Biotransformation. In the recent decades, with the increasing interest on gut microbiota, the interaction between gut microbiota and medication has come into sight. As a result, the concept of "pharmacomicrobiomics" is put forward, describing the influence of different gut microbiota on drug metabolism and action. A review of Sousa et al. provided a detailed overview of the metabolic interactions between gut microbiota and different drugs with distinct mechanisms including but not restricted to reduction, hydrolysis, removal of succinate group, and deacetylation [21], suggesting that the microbiota variations may induce specific biotransformation on different drugs through the alteration on drug structure by endogenous

enzyme modifications. The microorganism-mediated modifications may lead to either increased or decreased bioactivity and may further result in toxicity. As Lehouritis et al. stated, the coincubation of bacteria (*E. coli* and *Listeria welshimeri*) could cause different changes in the therapeutic efficacy of 30 tested drugs, with 6 increased and 10 decreased therapeutic activities [22].

A popular example of microbiota modifications on the bioactivity and toxicity of anticancer drug is the irinotecan (CPT-11). Serving as a prodrug in CRC therapy, irinotecan is able to induce genotoxicity to tumor cells after being converted into its active form SN-38 and then is detoxified by host enzyme. Nevertheless, irinotecan is still responsible for several dose-limiting intestinal toxicities, largely due to the biotransformation of gut microbiota-produced enzyme β-glucuronidases, resulting in an increased level of SN-38 in the colon [23]. Providing antibiotics and inhibiting the bacterial β-glucuronidases are proved to be effective protective methods for ameliorating intestinal adverse effects [24, 25]. Other examples of drug-microbiota interactions include the decreased activity of doxorubicin by *Streptomyces* cell extracts [26], the increased toxicity of fludarabine, and the activation of prodrug 6-methylpurine-2-deoxyadenosine (6MePdR) by *Salmonella* [27]. Conceivably, the research into drug-microbiota interaction that is more specific and individualized is on the way, holding potential for the development of antitumoral therapy with more precision and fewer toxicities.

3. The Effect of Microbiota on Cancer Therapy: An Insight into Specific Bacterial Strains in Antitumoral Therapeutic Strategies

3.1. Escherichia coli. *Escherichia coli* is a gram-negative bacterium that is believed to be potentially oncogenic. On the one hand, it could produce colibactin, a substrate with genotoxic potential on the host epithelium, including double-strand breaks, DNA cross-linking, and AT enrichment [12]. On the other hand, the chronic inflammation it induced could further promote tumorigenesis [28].

Apart from the oncogenic effect, growing evidence has suggested that the presence of *E. coli* could also alter the efficacy of anticancer therapy. The drug-microbiome interaction study demonstrated an impaired therapeutic effect of several chemotherapy drugs, including gemcitabine, vidarabine, and etoposide phosphate, with a decreased survival rates and elevated cytotoxicity in mice [22]. In addition, an increased level of *E. coli* in patients receiving immunotherapy often results in nonresponse to anti-PD-1 treatment, together with an elevation in the amount of other bacterial strains including *Bacteroides thetaiotaomicron* and *Anaerotruncus colihominis* [12]. Together, these research findings highlight a negative influence of *E. coli* in cancer treatment.

However, in the recent years, with the advent of genetic engineering technology, *E. coli* has been acknowledged as a promising bacterial vector due to its low cost and ease of cultivation. Notably, in the field of anticancer therapy, *E. coli* specifically shows its potential for precise targeted therapy as it could preferentially colonize in malignant tumor sites where it tends to be a hypoxic region with few vesiculations [29]; therefore, it is difficult for the chemotherapeutic drug delivery. By genetic engineering, *E. coli* is able to be tailored to express various agents according to the therapeutic needs, such as bacterial toxins, cytokines, or antibodies [30], thus stimulating a more precise antitumoral response around tumor site. Further investigations and experiments are currently on the way for the clinical use of engineered bacteria in various cancers and may broaden the options for medical interventions in the future.

3.2. Enterococcus hirae (248). *Enterococcus hirae* is a gram-positive bacterium colonizing in the small intestine and is viewed as a probiotic with anticancer property [10, 31]. It has been evidenced that the *E. hirae* is a specifically enriched commensal before treatment in non-small-cell lung cancer (NSCLC) patients who could response to therapy, indicating its role in predicting the clinical outcome [32].

During chemotherapy, the *E. hirae* translocation from the intestine to secondary lymphoid organs in response to cyclophosphamide could elicit the immune responses towards malignancies, favoring the increase in IFNγ^+ type 17 T helper (Th17) cells and CD8$^+$ T cells both systemically and in the tumor [10, 31, 33]. Based on this T cell stimulating capacity, the anticancer property of *E. hirae* is also tested in the immunotherapy settings with anti-PD-1 antibody, in which the reintroduction of *E. hirae* and *Akkermansia muciniphila* successfully restored the compromised efficacy of PD-1 blockade in antibiotic-treated mouse model, germ-free mouse model, and antibiotic-treated SPF mouse model recolonized with bacterial commensals in nonresponders represented with a suppressed tumor growth [32]. These evidences suggest the property of *E. hirae* in facilitating the efficacy of anticancer therapies.

In the review of Goubet et al., the authors summarized several modes of action by which *E. hirae* work to enhance anticancer therapy [31]. Apart from the translocation mechanism, *E. hirae* could also elevate the levels of polyamine spermidine which shifts the immune system towards a Th1-dependent antitumor response and favor the colonization of *Bifidobacteria* [31] whose properties will be discussed in the section below.

3.3. Bifodobacterium. The anticancer function of *Bifidobacterium* species is widely acknowledged. As a gram-positive bacterium, it has long been approved to be used as a safe and beneficial probiotic strain in dietary and health care products. According to a clinical trial, providing probiotics containing *Bifidobacteria* and *Lactobacillus* to colorectal cancer patients who had received surgical treatment 4 weeks ago efficiently lowered the circulating proinflammatory cytokines in the patient serum after 6 months of treatment, with the only exception of relatively unchanged level of IFN-γ [34].

The use of *Bifidobacteria* also shows a promising role in immunotherapy, in which the oral administration of *Bifidobacteria* strains (*Bifidobacterium breve*, *Bifidobacterium longum*, and *Bifidobacterium adolescentis*) is able to facilitate the therapeutic effect of anti-PD-L1 treatment [11]. It is disclosed that the increase in the relative abundance of

Bifidobacteria strongly favored the cytotoxic T cell response, leading to a reduced tumor growth in the tumor bearing mouse model [11]. Further analysis revealed that the *Bifidobacteria* provoke the immune response in host primarily by boosting the function of dendritic cells, consisting with previous research reporting the ability of *Bifidobacteria* in inducing DC maturation and eliciting the production of different cytokines [35]. It is also revealed that several gene transcription pathways that are associated with antitumor response are significantly enriched, including pathways responsible for cytokine-cytokine receptor interaction, T cell activation, and mononuclear cell proliferation [11]. Altogether, these findings highlight the anticancer immune capacity of *Bifidobacteria* and may guide the use of probiotic products for augmenting the efficacy of cancer therapy in the future.

3.4. Bacteroides. As a commensal bacteria species in the colon, the *Bacteroides* spp. could be viewed as a beneficial strain under normal circumstances. It actively participates in many important metabolic activities in the gut, serving as a source of nutrition and vitamins for host as well as other bacterial species [36]. The capsular polysaccharide A (PSA) of *Bacteroides fragilis* is a critical modulator for the stimulation and development of human immunity, with its immunomodulatory effects reflecting in eliciting $CD4^+$ T cells, regulating the balance of Th1/Th2, and also providing a barrier function against pathogenic invasion. The *Bacteroides* spp. is also a producer of SCFA and thus could exert its anti-inflammatory role in host [36]. Notably, a lot of researches have pointed out the facilitating effect of *Bacteroides* in cancer immunotherapy, especially during anti-CTLA-4 treatment. It is reported that the response to CTLA-4 blockade could not be observed in germ-free and antibiotic-treated mouse models, but the gavage of *B. fragilis* successfully reinstated the response. This is achieved through the stimulatory role of *B. fragilis* on Th1 and DCs, restoring a tumor-targeted immune response initiated by CTLA-4 antibody [37]. Functional studies further confirmed this observation, indicating the antitumor immunostimulatory capacity of *Bacteroides thetaiotaomicron*, *B. fragilis*, and *B. cepacia* species in the process of anti-CTLA-4 immunotherapy [37]. In addition, the adverse effects of CTLA-4 blockade could also be reduced by probiotic supply of *Bacteroides*. As Vétizou et al. reported, after oral gavage of *B. fragilis* and *Burkholderia cepacia*, the colitis induced by anti-CTLA-4 is efficiently improved in antibiotic pretreated mice [37]. In accord with this notion, it is also demonstrated in another research that the *Bacteroides* overrepresentation is the reason for ameliorated degree of CTLA-4-blockade-induced colitis [38]. These observations have provided researchers with a more comprehensive understanding of *Bacteroides* spp. and may hopefully lead to deeper investigations of probiotic use of this commensal bacteria species in the field of anticancer therapy in the future.

However, the *Bacteroides* spp. could also become pathogenic if translocated into other parts of the body due to impaired immunity, damaged intestinal mucosa etc. For instance, *B. fragilis* is considered a main cause of intra-abdominal abscesses [36]. The mechanisms for *Bacteroides* pathogenesis include virulence factors production (for example, the *Bfr* toxin fragilysin), as well as expression of oxidoreductases to induce oxidative stress in host [36]. In addition, the enterotoxigenic *Bfr* strain has been proved to specifically link to colorectal cancer initiation [36]. This points to the fact that although *Bacteroides* spp. is a commensal bacterial strain in human body and is endowed with many beneficial properties, the more amount of *Bacteroides* in the body is not representative to a better health condition.

4. Conclusions

Although cancer has been viewed as a devastating disease, fortunately, the recent advances in treatment technology have brought new breakthroughs in the anticancer therapy. Of which, the use of gut microbiota as a new research direction has been tested in several preclinical and clinical trials with promising results in facilitating the efficacy of treatment, increasing the number of responders, and overcoming the treatment-associated adverse effects. There are now several ways to modulate the composition of the gut microbiota, with technologies from oral feeding of probiotic supply to fecal microbiota transplantation, and many have already been approved for standardized clinical use. However, further research is still needed to identify more specific and deeper underlying mechanisms in the relationship between gut microbiota and anticancer management, and as different bacterial species is able to induce different clinical outcomes, it is also important to identify variability in host immune responses elicited by different subtypes in the same bacterial strain. In addition, how the gut microbiota mapping could be used as a predictive biomarker to measure the clinical outcomes of patients is currently on the way, which may contribute to a better overall outcome of patients and more specific clinical applications in the future. In short, based on these research findings on the gut microbiota, it is promising that precise regulation of bacterial composition could eventually become feasible and more standardized for anticancer treatment in the future.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

TC conceived the idea for the review and designed its framework. WL conducted the research and wrote the manuscript. Both authors edited the manuscript. Both authors have read and approved the final manuscript.

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