European Journal of Clinical Microbiology & Infectious Diseases (2018) 37:2235–2240
https://doi.org/10.1007/s10096-018-3374-8

REVIEW

Roles of intestinal microbiota in response to cancer immunotherapy

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Received: 3 August 2018 / Accepted: 4 September 2018 / Published online: 12 September 2018

Abstract

Cancer immunotherapy has been significantly effective on multiple cancers; however, there are still a distinct number of non-responding patients and various immune-related adverse events in responding patients. It is known that heterogeneity of intestinal microbiota may lead to different outcomes of therapy. Previous studies have reported that intestinal microbiota is probably attributed to influence the efficacy of cancer immunotherapy. Some intestinal bacteria could synergize with immune checkpoint blockade agents and optimize the immune response against multiple cancers. Therefore, understanding the roles of intestinal microbiota could help to improve the clinical efficacy of cancer immunotherapy. In this review, we first introduced the close relationships between intestinal microbiota and intestinal immune system. Then, we described the emerging evidences that intestinal microbiota responses to cancer immunotherapy. Finally, we briefly reviewed the technical development on intestinal microbiota research.

Keywords Intestinal microbiota · Intestinal immune system · Cancer immunotherapy · Adverse side · Research technology

Abbreviations

AMPs	Antimicrobial peptides
CAR	Chimeric antigen receptor
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
DCs	Dendritic cells
ICIs	Immune checkpoint inhibitors
LP	Lamina propria
mAbs	Monoclonal antibodies
NLRs	Nod-like receptors
PRRs	Pattern recognition receptors
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
REGIIIγ	Regenerating islet-derived protein 3γ
REGIIIβ	Regenerating islet-derived protein 3β
SCFA	Short-chain fatty acids
TLRs	Toll-like receptors
Tregs	T regulatory cells
TGF-β	Tumor growth factor-β

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Introduction

In recent years, cancer immunotherapy has become very successful against distinct metastatic malignancies [1–3], due in great part to the clinical success of immune checkpoint blockade and chimeric antigen receptor (CAR)-modified T cell therapy. Immune checkpoint inhibitors (ICIs) have improved the survival of cancer patients. The ipilimumab and tremelimumab blocking cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) have been evaluated in the treatment of melanoma [4], prostate [5], lung [6], and pancreatic [7] carcinomas and have demonstrated an overall survival benefit in cancer patients [8]. However, the functions of cytotoxic T cells are inhibited in the tumor microenvironment, which conduces to cancer cell immune evasion [9]. In recent years, blockade of programmed cell death 1 (PD-1, nivolumab and pembrolizumab) and its ligand programmed death ligand (PD-L1) performs higher response rates and more prolonged overall survival than blockade of CTLA-4 (ipilimumab) [10, 11]. In addition, an exciting new approach CAR-T cell therapy in the fight against cancer, which refines the design of CARs and improves the cellular manufacturing processes with the purpose of delivering safe and efficacious therapeutic T cells, is bringing the promising therapeutic platform for more cancer patients.

Unfortunately, the beneficial effects of these immunotherapy strategies are seen only in a subgroup of patients [12], and these ICIs treatments are closely associated with various immune-related adverse events. The most common immune toxicities include colitis, diarrhea, thyroid dysfunction, dermatologic event, liver disorder, and lung disorder [13]. Although these side effects have become relieved to some extent by using corticosteroid therapy, new effective indicators of response and toxicity are necessary to improve the compliance to immunotherapy. The recent flurry of scientific studies on the effects of intestinal microbiota in response to cancer immunotherapy opens up an entirely novel approach to the treatment of cancer diseases [14–16]. The intestine faces constant challenges from food antigens, pathogens, and commensals and has to make appropriate responses precisely and quickly. The intestinal microbiota is important for human metabolism such as production of short-chain fatty acids, essential vitamins, and amino acids [17]. Intestinal microbiota is also a key for the development of the mucosal immune system [18]. Therefore, intestinal microbiota appears a very promising area of research in modulating the immune system and finding an impact in anti-tumor immunotherapy. The purpose of this review is to help us better understand the role of intestinal microbiota and improve the efficacy in cancer immunotherapy by the regulation of intestinal microbiota.

Intestinal microbiota and intestinal immune system

The intestinal microbiota plays essential roles in modulating the intestinal immune response to keep intestinal immune homeostasis [19]. Intestinal microbiota is capable to module host physiology and/or nutritional status and influences not only the intestine but also distant organs [20].

Intestinal barrier

Usually, the spatial interactions between intestinal microbiota and intestinal immune system can be divided into three functional layers. Facing to the intestinal lumen, the first layer, rich in mucus, can also be divided into another two sublayers: the outer sublayer and the inner layer. The outer sublayer is very abundant in microbiota, while the inner layer has high concentration of bactericidal antimicrobial peptides (AMPs) and secretory IgA. The second layer is made up of a monolayer of intestinal epithelial cells (IECs), which are mainly composed by goblet cells, absorptive enterocytes, and enteroendocrine cells, paneth cells, M cells, and so on [21, 22]. IECs play a key role in separating the internal body organs from the outside environment by the formation of tight junctions and secretion of mucus and AMPs [21]. IECs express pattern recognition receptors (PRRs), including nod-like receptors (NLRs) and toll-like receptors (TLRs) [23]. The production of some types of AMPs, like angiogenin-4, regenerating islet-derived protein 3γ (REGIIIγ), and regenerating islet-derived protein 3β (REGIIIβ), is influenced by commensal microbes in a toll-like receptor-dependent way [21]. In IECs layer, paneth cells are the leading producer of AMPs [24]. The M cells are a very important cell type, because these cells work directly with the immune system [21]. The third layer is formed by lamina propria (LP) and mesentery. Microbe-associated molecular patterns from colonizing bacteria are sensed by PRRs or dendritic cells (DCs) that activate T and B cells in isolated lymphoid follicles. DCs that capture antigens through IECs or from LP migrate to mesenteric lymph node to induce the differentiation of effector T cells [25]. The interactions of intestinal microbiota, intestinal epithelium, and mucosal immune system lead to a local and systemic homeostasis.

Interactions of intestinal microbiota and intestinal immune system

The gastrointestinal tract is inhabited by various microbes including commensal bacteria and pathogenic bacteria. Usually, commensal bacteria are beneficial for the host, while pathogenic bacteria are able to cause problems, such as intestinal inflammation and invasiveness. The intestinal immune system shapes the intestinal microbiota composition, and the latter regulates the intestinal immune system responses [26]. In a symbiosis context, microbe-associated molecular patterns constantly stimulate IECs to secrete some immunological mediators, such as IL-33, IL-25, and tumor growth factor-β (TGF-β), which induce the development of tolerogenic macrophages and tolerogenic DCs [25, 27]. And tolerogenic DCs could produce TGF-β and retinoic acids that activate the development of T regulatory cells (Tregs). Therefore, the intestinal immune system associated with intestinal microbiota could establish and maintain an anti-inflammatory environment through tregs, macrophages, and tolerogenic DCs. In a dysbiosis context, the pathogenic bacteria overcome commensal bacteria and disrupt the regulated anti-inflammatory environment. This unstable state can induce IECs and activate dendritic cells and macrophages to secrete inflammatory cytokines (IL-1β, Il-6, IL-12, and IL-23). These cytokines stimulate the development of TH1 cells and TH17 cells leading to chronic inflammation [27]. Furthermore, intestinal microbiota could produce high levels of endotoxins, which will cause systemic inflammation once in the bloodstream, resulting in the progression of many human diseases.

Recent studies have focused on the interactions between the intestinal microbiota and the immune system. Masahata et al. found that IgA-secreting cells were closely associated with the maintenance of intestinal microbial homeostasis and contributed to shaping the healthy intestinal microbial community, indicating that the development of immune system had a close accordance with intestinal microbiota [28]. Atarashi et al. demonstrated that a mixture of *Clostridia* strains from the human intestinal microbiota was able to induce the accumulation of Tregs and IL-10 production in intestine [29]. Cording et al. concluded that intestinal microbial stimulus locally influenced the Treg proliferation and systemically affected conventional $CD4^+$ T cells [30]. The intestinal microbiota undoubtedly influences the regulatory cells; however, the mechanisms induced by microbes influencing the development of Tregs remain unknown. Obata et al. [31] explored the changes in IL-2 expressing $CD4^+$ T cells and $FoxP3^+$ Treg cells by inoculating germ-free mice with commensal microbiota. The results found that changes of IL-2^+ $CD4^+$ T cells were different from Treg cell expansion, suggesting that commensal microbiota stimulated the development of the Tregs in an IL-2-dependent manner. In addition, some studies tried to identify the metabolites of intestinal microbiota to influence the immune system and regulate homeostasis. Smith et al. [32] found that germ-free mice had a series of immunological problems, and the abundance of three types of short-chain fatty acids (SCFAs: acetic acid, butyric acid, and propionic acid) was significantly decreased. After treating the germ-free mice with SCFAs for 3 weeks, these mice showed an increasing in frequency and number of colonic Tregs. Therefore, SCFAs metabolized by intestinal microbiota played a key role in maintaining homeostasis through Tregs. The result was also confirmed by the study of Furusawa et al. [33], who found that the luminal concentrations of SCFAs were positively correlated with the number of regulatory cells in the colon.

As the conclusions described above, intestinal microbiota and immune system interact continuously to maintain a complex dynamic equilibrium for host health. A complete understanding of the relationship between intestinal microbiota and intestinal immunity is very important for the treatment of human many diseases.

Intestinal microbiota influences the efficacy of cancer immunotherapy

Intestinal microbiota has ascended to prominence as important modulators of host immunity and has made the possibility of influencing the outcome of cancer immunotherapy. Table 1 lists some researches about intestinal microbiota in response to cancer immunotherapy. In this following, we summarized some studies about intestinal microbiota influencing the efficacy of cancer immunotherapy.

Intestinal microbiota in response to CTLA-4-based immunotherapy

Different from cytotoxic therapies, ICIs regulate tumor changes via enhancing host immune activation. Antibodies targeting CTLA-4 have been successfully used as cancer immunotherapy. Ipilimumab is a fully human monoclonal antibody directed against CTLA-4, approved as the first drug for improving the overall survival of patients with metastatic melanoma [8]. Previous studies have addressed the role of intestinal microbiota in immunomodulatory effects of CTLA-4 blockade [34]. Marie Vétizou et al. found tumors in antibiotic-treated or germ-free mice did not respond to CTLA-4 blockade; however, this defect was overcome by gavage with *Bacteroides*

Table 1 Clinical evidences that the key intestinal microbes are associated with the efficacy of cancer immunotherapy

Antineoplastic treatment	Tumor	Relevant intestinal microbes	Publication date/reference
Anti-PD-L1 mAbs	Melanoma	*Bifidobacterium*	2015/[17]
Anti-CTLA-4 mAbs (ipilimumab)	Melanoma	*Bacteroides thetaiotaomicron*, *Bacteroides fragilis*	2015/[34]
Anti-CTLA-4 (ipilimumab) and/or anti-PD-1 (nivolumab) mAbs	Melanoma	*Faecalibacterium prausnitzii*, *Dorea formicigenerans*	2017/[35]
Anti-CTLA-4 (ipilimumab) and/or Anti-PD-1 (nivolumab), or PD-1 (pembrolizumab) mAbs	Melanoma	*Faecalibacterium prausnitzii*, *Bacteroides thetaiotamicron*, *Holdemania filiformis*, *Dorea formicogenerans*, *Bacteroides caccae*	2017/[36]
Anti-PD-1 or anti-PD-L1 mAbs	Non-small cell lung cancer/renal cell carcinoma/urothelial carcinoma	*Akkermansia muciniphila*	2018/[37]
Anti-PD-1 or anti-CTLA-4 mAbs	Melanoma	*Bifidobacterium longum*, *Collinsella aerofaciens*, *Enterococcus faecium*	2018/[38]
Anti-PD-1 (pembrolizumab) mAbs	Melanoma	*Ruminococcaceae*	2018/[39]

mAbs monoclonal antibodies

fragilis, by adoptive transfer of *Bacteroides fragilis*-specific T cells, or by immunization with *Bacteroides fragilis* polysaccharides [34]. This study indicates that *Bacteroidales* plays an important role in the immunostimulatory effects of CTLA-4 blockade. Chaput et al. reported that *Faecalibacterium* and other *Firmicutes* were closely associated with beneficial clinical response, but a higher representation of *Bacteroides* genus in metastatic melanoma patients had a poor response to anti-CTLA-4 treatment [35]. The conclusion was inconsistent with the results of Marie Vétizou trial in mouse models [34]. The discrepancy is mainly ascribed to different models. Apart from this, it is difficult to exclude other microbes interfering results in mouse experiment. Therefore, further studies should be carried out to evaluate the effect of CTLA-4-based immunotherapy on intestinal microbiota.

Intestinal microbiota in response to PD-1/PD-L1-based immunotherapy

Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 lead to sustained clinical responses in cancer patients [40]. Routy et al. found that abnormal intestinal microbial composition caused primary resistance to ICIs [37]. The relative abundance of *Akkermansia muciniphila* significantly affected the clinical responses to ICIs, proved by oral supplementation with *Akkermansia muciniphila* for non-responders to restore the efficacy of PD-1 blockade [37]. Mastson et al. analyzed fecal samples from metastatic melanoma patients before anti-PD-1 immunotherapy based on 16S rRNA sequencing, metagenomic shotgun sequencing, and quantitative polymerase chain [38]. The results suggested that commensal microbiome including *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium* could have important impacts on anti-tumor immunity. Frankel et al. showed that melanoma patients who responded to ICIs were enriched with *Bacteroides caccae* using metagenomic shotgun sequencing method [36]. Wargo et al. also found that intestinal microbial diversity and composition in metastatic melanoma patients that responded to the anti-PD-1 therapy were significantly different from that in non-responding patients [39]. The responders had higher alpha diversity and relative abundance of *Ruminococcaceae* bacteria, and the non-responders had lower diversity and higher relative abundance of *Bacteroidales* [39]. In addition, Sivan et al. explored melanoma growth in mice harboring distinct commensal microbiota and found *Bifidobacterium* could promote anti-tumor immunity and facilitate anti-PD-L1 efficacy [16]. Above all these findings, intestinal microbiota could improve PD-1 and PD-L1 immunotherapy by regulating the immune response. Therefore, keeping the intestinal microbiota healthy could help cancer patients improve therapeutic efficacy.

Furthermore, CAR-T cell therapy has the remarkable potential to become promising therapeutic platform especially for a few cancer patients with hematologic tumors in recent years. However, adoptive T cell therapy is still in its infancy, and a number of challenges need to be considered to provide safe and reliable cellular products. Up to now, there is no related study about intestinal microbiota in response to the efficacy of CAR-T cell therapy.

Immune-related adverse events involved in intestinal microbiota

Blockades of CTLA-4 and PD-1 often lead to immune-related adverse events that are mostly exposed to intestinal microbiota [41]. During CTLA-4 and PD-1 blockade treatment, intestinal epithelial cell injury results in the loss of integrity of intestinal barrier. Some commensal bacteria such as *Enterococcus hirae* can influence systemic inflammation by destroying intestinal barrier into secondary immune organs even tumor bed [42]. Marie Vétizou and colleagues identified that two species from *Bacteroidales* and *Burkholderiales* order significantly reduced the histopathological colitis associated with anti-CTLA-4 therapy in mice model, which was a common, high-risk, immune-related adverse event [34]. Krista Dubin et al. found that the *Bacteroidales* species were closely linked with decreased incidence of colitis in patients with metastatic melanoma who have undergo ipilimumab treatment [43]. However, it also reported that certain *Bacteroidales* species in the gut were correlated with colitis [44]. One convincing reason is that the anatomical structures of gastrointestinal tract and intestinal wall linings in human and mouse are significantly different [45]. Another reason is that many intestine-colonizing microbes in mice are not found in humans [46]. Additionally, individual diet and lifestyle contribute to the intestinal microbiota in response to immunotherapy [47, 48].

New techniques on intestinal microbiota research

Much of our current understanding of interactions between intestinal microbiota and immune system has been mainly acquired from studies of germ-free animals. However, the composition of human and animal intestinal microbiota can be defined from polymorphisms of bacterial genes. Therefore, technological advances play great roles in facilitating studies of complex intestinal microbiota and their functions. The DNA sequencing technology (next-generation sequencing, metagenomic) improvements have identified potential functions of microbes in human gut [49, 50]. However, a vast majority still have no known functions, reflecting the great diversity and biochemical potential of microbiota remaining to be discovered. The mRNA sequencing (metatranscriptomic), revealing which genes are expressed by specific organisms from spatial and temporal scales, has offered a wealth of knowledge about the

expression of microbial genes in human gut [51]. The nucleic acid sequencing has helped to explore and understand microbial phylogenetic and functional compositions in human intestinal microbiomes [49, 52]; however, it is also desirable to know which proteins (metaproteomic) and metabolites (metabolomic) play key roles in performing special functions. These proteins and metabolites produced by microbes were measured by mass spectrometry, which had high sensitivity, resolution, and throughput in providing metaproteomic or metabolomic measurements. Furthermore, additional technologies such as gas-phase ion mobility spectrometry and liquid chromatography separations are also being used to identify the more proteins and metabolites.

Metagenomic, metatranscriptomic, mass spectrometry-based metaproteomic and metabolomic gas-phase ion mobility spectrometry and liquid chromatography separations have offered a deeper understanding of composition and function of microbiomes. However, there are still many challenges to be addressed, such as extraction of biomolecules from complex environmental samples (human gut), assembly of complete genomes, statistical and mathematical models to integrate the data, and sufficient storage and analysis options for meta-data to provide meaningful biological insights.

Conclusions

Mounting evidences indicate that the intestinal microbiota influences cancer patients in response to immunotherapy, including the therapy efficacy and side effects. Intestinal microbiota probably becomes a novel biomarker of immune response. However, it still requires extensive studies, development, and testing, especially applying all acquired knowledge to transfer from mice models to human beings. Furthermore, the technological and computational improvements will contribute to a better understanding of how cancer immunotherapy affects microbial functions and facilitate human health strategy improvement. Summing up, regulating the intestinal microbiota probably helps to improve tumor control, augment immune responses, and enhance the efficacy of immunotherapy in the demanding fight against cancer.

Acknowledgements The assistance of the staff is gratefully appreciated.

Funding This study was supported by the funding from Project funded by China Postdoctoral Science Foundation (2016M602094), Qingdao Application Research Project (2016047), and Qingdao People's Livelihood Science and Technology Program (16-6-2-3-nsh).

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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