Gut microbiota reshapes cancer immunotherapy efficacy: mechanisms and therapeutic strategies

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Jindong Xie, Manqing Liu, Xinpei Deng, Yuhui Tang, Shaoquan Zheng, Xueqi Ou, Hailin Tang, Xiaoming Xie, Minqing Wu, Yutian Zou. 2023. Gut microbiota reshapes cancer immunotherapy efficacy: mechanisms and therapeutic strategies. **iMeta** e156. https://doi.org/10.1002/imt2.156

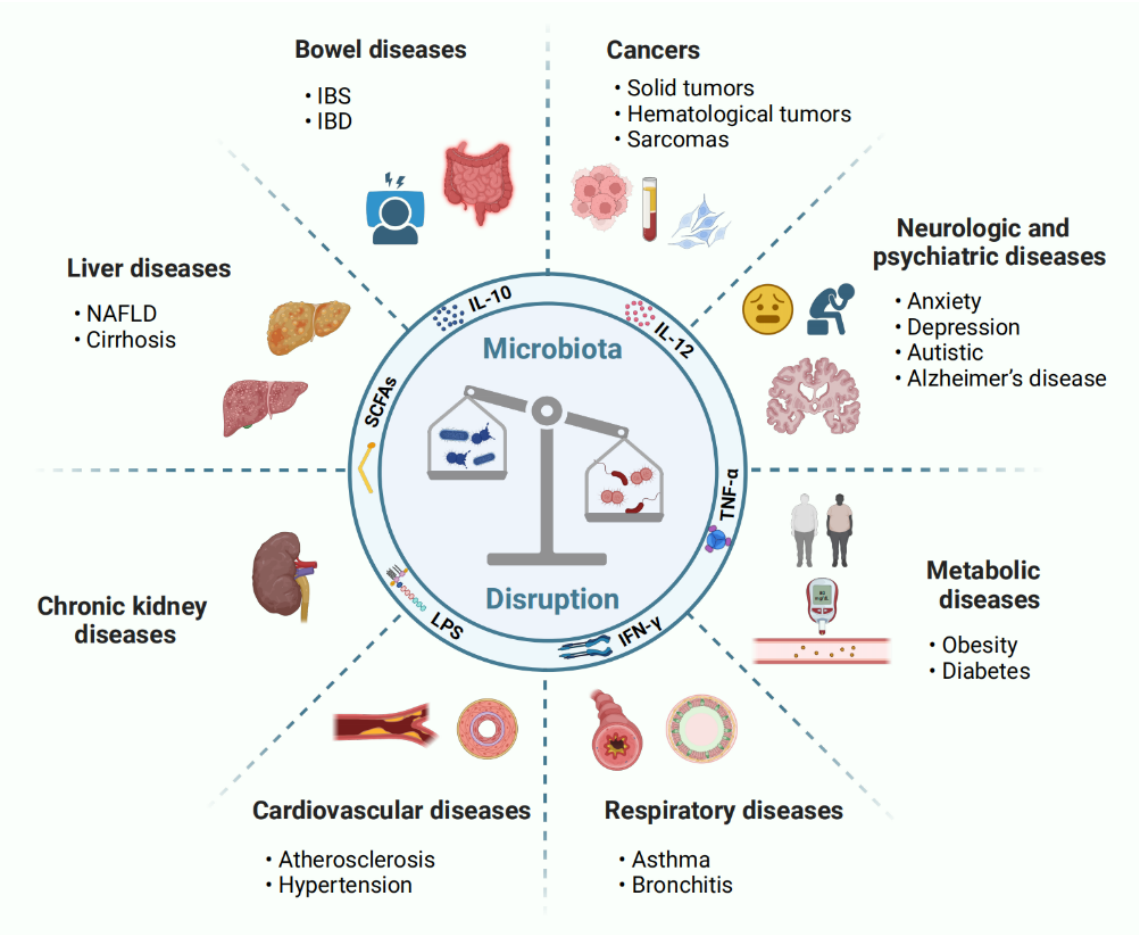
Introduction

Gut microbiota has an intricate relationship between cancer and anticancer therapies in a balance between proinflammation and anti-inflammation function. Previous studies have demonstrated that the diversity and composition of gut microbiota were associated with the heterogeneity of immunotherapy therapeutic effects.

Immunotherapy has dramatically changed the treatment landscape of cancers. Different from conventional anticancer therapies like chemotherapy and radiotherapy, it retards tumor growth indirectly by unleashing and enhancing host anti-tumor immune response. However, immunotherapy is only effective for a small share of patients, and the treatment paradigms are complicated by immune-related adverse effects, inhibiting the rapid development and clinical application of immunotherapy.

Emerging evidence has suggested that gut microbiota and its metabolites can significantly contribute to the efficacy and/or toxicity of immune-related interventions. Thus, manipulating gut microbiota towards the dominance of “beneficial” bacteria might be a new therapeutic strategy and a novel biomarker to improve and predict the clinical outcomes of cancer patients receiving immunotherapy.

Introduction



1.The-cancer-microbiota-immune axis

The dual role & immunomodulation function of gut microbiota in cancer

Gut microbiota includes carcinogenesis by producing toxic metabolites, inducing inflammation milieu, and suppressing anti-tumor immunity, which leads to genomic instability, DNA damage, and immune escape in tumor tissue. Regulating hormones in circulation or through a reciprocal route called the gut-brain axis by gut microbiota induces dysplasia in distal organs and systems outside the gastrointestinal tract

Conversely, intact intestinal microbiota served as a protective role against cancer. Gut microbiota might retard tumor growth partially through altering microbial composition in tumor and shaping the TME. It can also maintain intestinal and immune homeostasis through modulation of intestinal stem cells, and improve immune surveillance through tumor adjuvanticity and antigenicity.

2.Impact of the gut microbiota on cancer immunotherapy

Involvement of gut microbiota to cancer immunotherapy

Through the gut wall where immune cells are located, the gut microbiota interacts with the immune system, which allows it to affect gut immunity as well as immune responses in distal mucosal sites via circulation and systemic metabolism. Anti-tumor therapies like chemotherapy, radiotherapy, and immunotherapy can damage the integrity of the physical gut epithelial barrier, causing translocation or accumulation of specific microbiota, which leads to alteration in the constitution of the commensal microbiota.

Dysbiosis of intestinal contents could also affect the clinical outcome of cancer immunotherapy since gut microbiota and host immunity are mutualistic. It is common practice to prescribe antibiotics to patients undergoing cancer treatments to prevent or alleviate opportunistic infections. Beyond its antibacterial effects, evidences have shown that antibiotics are the most common cause of dysbiosis, leading to a detrimental impact on T cell-based immunotherapies by changing the composition or decreasing the diversity of the gut microbiota.

Results

2. Impact of the gut microbiota on cancer immunotherapy

Relationship between gut microbiota composition and efficacy of immunotherapy

- Immune checkpoint inhibitor (ICI) therapy

Many preclinical and clinical studies have suggested that interindividual differences in the composition of the commensal microbiota might account for the significant heterogeneity in the success of ICI treatments. studies found that decreased diversity or richness of fecal bacterial composition was correlated with lower response rate and worse patient survival. In addition to the diversity of the gut microbiota, further studies have identified that the accumulation of specific bacteria species or strains in the gut microbiota ecosystem was also associated with higher therapeutic efficacy of immunotherapies and enhanced anti-tumor T cell immunity.

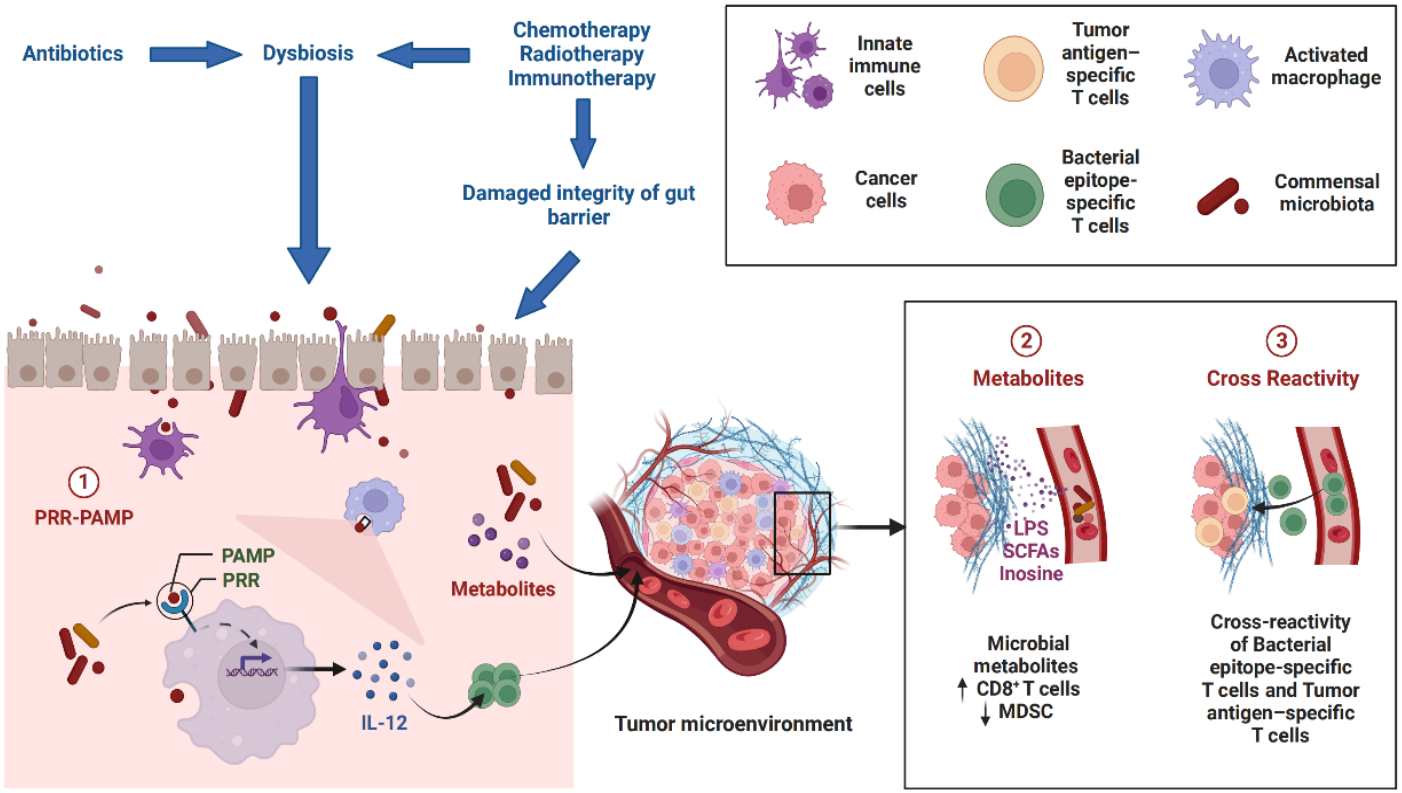
- Chimeric antigen receptor T cells (CARTs) and allogeneic hematopoietic cell transplantation (allo-HCT)

ICI treatment has achieved great success in numerous solid tumor types. However, for hematological malignancies, CARTs targeting CD19 and allo-HCT have been demonstrated as prototype and innovation of T cell-based anticancer therapies, respectively. A growing understanding of how gut microbiota composition affects allo-HCT and CART immunotherapy is emerging.

Results

2. Impact of the gut microbiota on cancer immunotherapy

Relationship between gut microbiota composition and immune-related toxicities

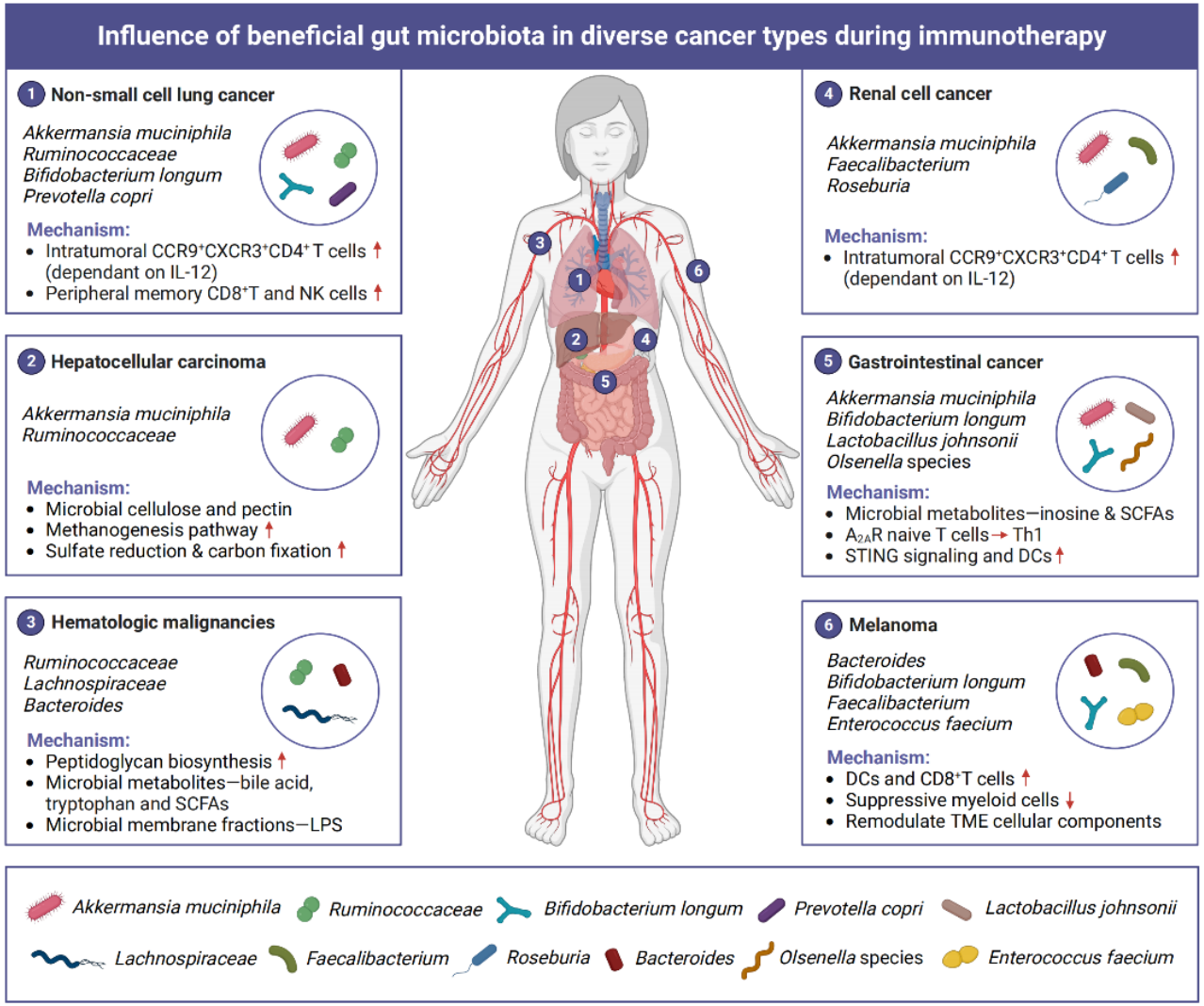


- Anti-cancer therapies can increase the permeability of gut epithelial, translocation of bacteria and dysbiosis. During cancer therapy, antibiotics are sometimes used, which can also lead to disruption of gut microbiota.
- The mechanism of immunostimulation by gut microbiome includes ligation of PRR and PAMP, release of microbial metabolites such as SCFAs, LPS and inosine, and cross-reactivity of bacteria epitope-specific T cells and tumor antigen-specific T cells.

Abbreviations: PRR, pattern recognition receptor; PAMP, pathogen-associated molecular patterns; LPS, Lipopolysaccharides; SCFAs, short-chain fatty acids

Results

3.Applications of gut microbiota: serving as new therapeutic tools and biomarkers for immunotherapy



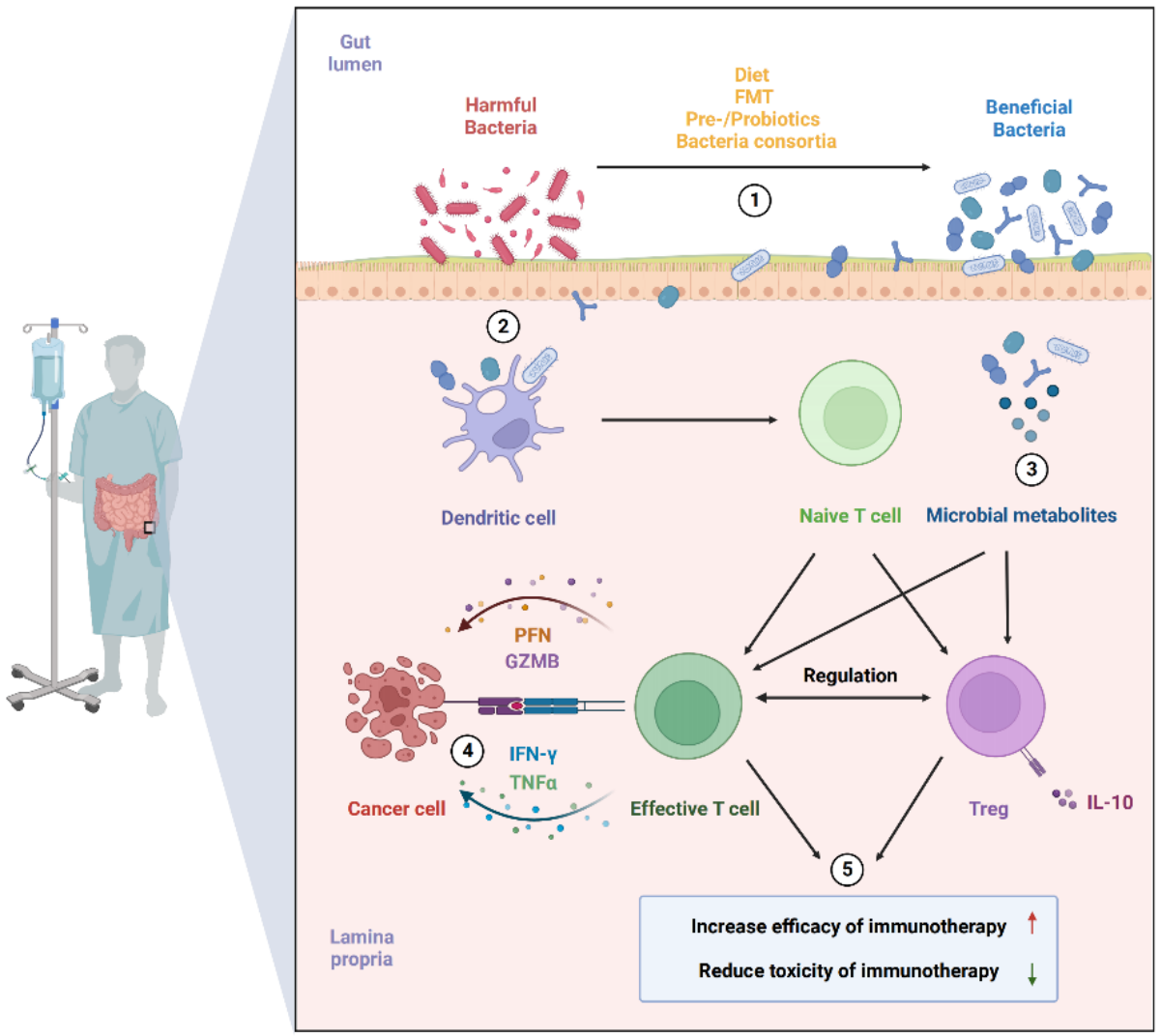
New therapeutic strategies to improve cancer immunotherapy

- Dietary intervention,
- Fecal microbiota transplantation (FMT)
- Defined commensal strains
- Prebiotics and probiotics

Novel biomarkers to predict host response to immunotherapy

Fingerprints were detected between responders and non-responders to ICI therapies based on gut microbiota profiling, indicating the potential of utilizing gut microbiota composition and its metabolites to predict the clinical outcomes of immunotherapy in a minimal invasive and easy way.

Summary



Highlights:

- Gut microbiota has been acknowledged as key regulators in host-mediated anticancer immune response especially during immunotherapy, and antibiotics-induced dysbiosis often leads to resistance to immunotherapy and poor clinical outcomes.
- We reviewed the commensal bacteria profiles associated with responders to immunotherapy in various cancer types, characterized by a high diversity with abundance of specific species, which may help predict patients' sensitivity to immunotherapy before treatment.
- We propose that gut microbiota act as the future therapeutic target and adjuvant in personalized anti-cancer regimen, and reviewed the current dilemma and potential strategies to manipulate gut microbiota towards "beneficial bacteria".

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