

eGastroenterology Gut microbiota and immune alteration in cancer development: implication for immunotherapy

Harry Cheuk Hay Lau, Xiang Zhang, Jun Yu

To cite: Lau HCH, Zhang X, Yu J. Gut microbiota and immune alteration in cancer development: implication for immunotherapy.

eGastroenterology 2023;1:e2023. doi:10.1136/egastro-2023-100007

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/egastro-2023-100007>).

Received 20 November 2022

Accepted 19 January 2023

ABSTRACT

Human gastrointestinal tract harbours trillions of microbes to form the gut microbiota. Through interacting with host cells, gut microbes play critical roles in host physiology and function. On the other hand, an altered or dysbiotic microbiota is now well acknowledged for contributing to cancer development and progression. Since the last decade, immunotherapy has risen as a promising and novel means to fight against cancer. Meanwhile, accumulating studies have clearly revealed the close association of gut microbiota with immunotherapy efficacy, suggesting the feasibility of modulating microbiota to improve treatment responsiveness. In this review, we present the current evidence elucidating the interplay between gut microbiota and immune system in the development of several cancers including colorectal cancer, hepatocellular carcinoma and melanoma. We also discuss how the gut microbiota impacts immune checkpoint inhibitors, one of the most common approaches of immunotherapy, and explore approaches that aim to harness the gut microbiota to improve treatment efficacy. Overall, investigations on the relationship between microbiota and cancer immunotherapy can have important clinical significance, potentially leading to the development of more potent and effective cancer therapeutics in the near future.

INTRODUCTION

Human body is colonised by a vast number of microbes to form an ecological community known as the microbiota, which is comprised of bacteria, viruses, fungi and archaea.¹ These microbes are closely associated with physiology and function of the human body, especially in the gastrointestinal tract.² Considering to be the second genome in humans, the gut microbiota has received tremendous research attention with the recent advance in metagenomic sequencing.³ Under normal conditions, the gut microbiota is maintained in homeostasis, yet it is readily affected by various environmental factors including diet and antibiotic use.⁴ Once its composition and function become imbalanced (commonly termed as dysbiosis), the gut microbiota may contribute to the pathogenesis of various diseases,⁵ including cancer.

Numerous research has identified the impacts of gut microbiota on the development of various cancers, such as colorectal cancer (CRC), melanoma and hepatocellular carcinoma (HCC).⁶ In general, the gut microbiota in patients with cancer is significantly altered with the enrichment of pathogenic microbes (eg, *Helicobacter pylori* for gastric cancer and *Fusobacterium nucleatum* for CRC), leading to the acceleration of cancer development and progression.⁷

Meanwhile, increasing evidence showed that the gut microbiota could affect the responsiveness and efficacy of cancer treatment.⁸ Immunotherapy, particularly immune checkpoint blockade which uses monoclonal antibodies to target immune checkpoints, has emerged since the last decade and demonstrated great therapeutic efficacy in patients with different types of cancer. In general, as immunotherapy aims to enhance host antitumour immunity, it can eliminate tumour cells more specifically than traditional treatments with less damage to normal cells.⁹ To date, a few immune checkpoint inhibitors (ICIs; for example, nivolumab, pembrolizumab) have received Food and Drug Administration approval to treat several types of gastrointestinal cancer. Notably, given the intricate interaction between host immunity and gut microbiota,¹⁰ it is reasonable to speculate that microbes can influence ICIs efficacy. Indeed, more and more studies have suggested that the gut microbiota plays a crucial role in shaping the efficacy of immunotherapy.^{11–13} In this review, we will discuss the effect of microbiota on cancer immunotherapy and harnessing gut microbiota in improving response to immunotherapy.

INTERPLAY BETWEEN GUT MICROBIOTA AND IMMUNE SYSTEM IN CANCER DEVELOPMENT

Under normal or non-cancerous conditions, the gut microbiota is closely associated with the maintenance of structure and function



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Institute of Digestive Disease and the Department of Medicine and Therapeutics, State Key Laboratory of Digestive Disease, Li Ka Shing Institute of Health Sciences, CUHK Shenzhen Research Institute, The Chinese University of Hong Kong, Hong Kong, China

Correspondence to

Professor Jun Yu;
[junyu@cuhk.edu.hk](mailto:juny@cuhk.edu.hk)

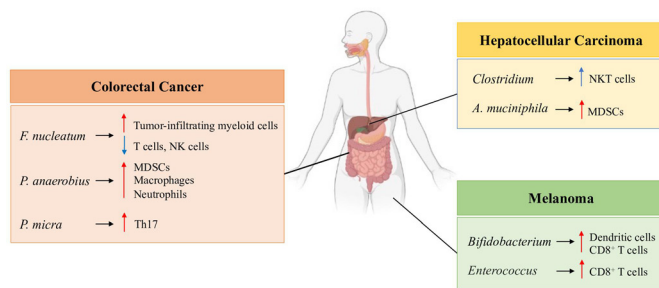


Figure 1 Interplay between gut microbiota and host immunity in cancer. Different microbes interact with host immune cells in the development of CRC, HCC and melanoma. Some of these interactions are pro-tumourigenic (labelled in red), while the others are against cancer progression (labelled in blue). CRC, colorectal cancer; HCC, hepatocellular carcinoma; MDSCs, myeloid-derived suppressor cells; NKT, natural killer T cells.

of the mucosal immune system and helps to defend any invaded pathogens.¹⁴ However, in the tumour microenvironment, tumour cells evade the attack of immune system via different mechanisms, including the upregulation of immunosuppressive ligands on the surface of tumour cells, and the release of T cell suppressors (eg, arginase) to inhibit intratumoral infiltration of effector T cells.¹⁵ These immunosuppressive features are indeed significant barriers to overcome, while they also provide rationale for the development of therapeutic approaches particularly ICIs that specifically target the antitumour immunity.¹⁶ In this section, we will introduce the mechanism of antitumour immunity and the role of dysbiotic microbiota in tumourigenesis in various cancer types (figure 1).

Antitumour immunity and tumour microenvironment

The principle of immunotherapy is based on the fundamental concept, ‘cancer immunoediting’, stating that the immune system can be protective to the host meanwhile prompting cancer progression.¹⁷ During immunoediting, the immune system shapes the immunogenicity of tumours in three phases—elimination, equilibrium and escape.¹⁷ In the first phase, both innate and adaptive immune systems detect and destroy early tumours before they become clinically visible.¹⁷ To eliminate tumour cells, dendritic cells are required to cross-present tumour neoantigens to naïve T cells, thereby subsequently allowing their activation.¹⁸ These activated effector T cells then release interferon- γ to mediate antitumour effects.¹⁸ Moving on to the equilibrium phase, the balance of antitumour immunity starts sloping to immune-mediated tumour dormancy, in parallel with tumour growth.¹⁶ Due to the pressure on antitumour immunity, tumour cells with less immunogenicity are more likely to survive the immune attack. These survived tumour cells can then undergo genetic and epigenetic modifying, leading to increased resistance of immune recognition in the tumour microenvironment and eventually immuno-suppression,¹⁹ whereas the balance between tumour-suppressing and tumour-promoting effects of antitumour

immunity is mainly mediated by adaptive but not innate immune system.¹⁹ Finally, given the accumulation of less immunogenic tumour cells, the antitumour immunity becomes exhausted and hence ineffective to eliminate tumour cells. Tumour cells evade immune recognition via multiple mechanisms, including the loss of surface markers such as tumour neoantigens and co-stimulatory molecules which can be readily recognised by immune cells. These mechanisms collectively shift the balance of antitumour immunity from being protective of the host towards favouring tumour progression.²⁰

A solid tumour consists of different cells with tumour cells being the predominant cell type, while these tumour cells interact immune cells and their derivatives to form the tumour microenvironment.²¹ There are a variety of immune cell types in the tumour microenvironment. Some of them such as natural killer (NK) cells and active CD8⁺ T cells stimulate antitumour immune response to directly eliminate or induce cytotoxicity on tumour cells.²² In contrast, other immune cells suppress the antitumour immunity. For example, tumour-associated macrophages can differentiate into the anti-inflammatory M2-like phenotype, thereby inhibiting the antitumour function of cytotoxic CD8⁺ T cells and promoting intratumoral infiltration of immunosuppressive regulatory T cells (T_{reg}).²³ Meanwhile, myeloid-derived suppressor cells (MDSCs) can coordinate with other immune cells to maintain an immunosuppressive microenvironment, which in turn favours the survival of tumour cells.²⁴ In general, antitumour immunity is often over-ridden by tumour cells as a mechanism of immunoediting, while recent evidence has illustrated the crucial crosstalk between microbes and immune cells in cancer development.

Gut microbiota and immune alteration in CRC

Among all different cancer types, the correlation between the gut microbiota and CRC is undoubtedly being the most extensively studied. For instance, our team previously identified that the transplantation of gut microbiota from patients with CRC could induce colorectal tumourigenesis in conventional and germ-free mice by promoting pro-inflammatory cytokines expression and increasing helper T cells (Th)-1 and Th17 infiltration into the colon.²⁵ Th17 in the small intestinal lamina propria could also be induced by gut-segmented filamentous bacteria accompanied with the release of serum amyloid A, a protein acting on dendritic cells to promote Th17 differentiation.²⁶

Several bacterial species that are capable of promoting colorectal tumourigenesis have been identified. *F. nucleatum* recruits tumour-infiltrating myeloid cells, which can promote tumour progression.²⁷ Moreover, *F. nucleatum* inhibits T cells and NK cells, which contribute to CRC progression.²⁸ *Peptostreptococcus anaerobius* is a pathogenic bacterium that is highly enriched in patients with CRC. Consistent to the clinical findings, *P. anaerobius* could induce a higher incidence of intestinal dysplasia in CRC mouse models.²⁹ Through single-cell sequencing,

P. anaerobius was found to be able to suppress the host antitumour immunity, with the expansion of MDSCs, tumour-associated macrophages and neutrophils associated with inflammation and tumourigenesis.³⁰ *Parvimonas micra* is another pathogenic bacterium that is enriched in patients with CRC, and it has been identified by several studies as an independent risk factor of CRC with poor survival. Mechanistically, *P. micra* could induce the differentiation of CD4⁺ T cells to Th17 phenotype and increased Th17 cells-secreted cytokines, thereby promoting inflammation.³¹ Collectively, these pathogenic bacteria promote CRC development through regulating immune microenvironment.

Gut microbiota and immune alteration in HCC

The gut microbiota not only affects the local intestines, but can also impact distal organs including liver through the gut–liver axis.³² The human liver has a double blood supply: the hepatic artery from the coeliac axis, and the portal vein bringing venous blood from the intestines and spleen. Of note, the portal venous blood flow from the mesenterium accounts for 75% of the blood supply to the liver.³³ In healthy or non-disease conditions, the gut–liver axis is maintained by the intestinal barrier, which strictly limits the access of gut bacteria and their derivatives into the portal vein circulation. However, the intestinal barrier can be interrupted by (1) dysbiosis or abnormal composition of the gut microbiota, (2) an impaired mucosal barrier and (3) loss of integrity of the immune system, leading to increased intestinal permeability.³² As a consequence, gut bacteria and their derivatives now have easier access to the portal vein circulation and further reaching the liver. On the other hand, some endotoxins including lipopolysaccharide (LPS) and peptidoglycans can accumulate in the liver, eventually contributing to hepatic inflammation and pathogenesis of liver diseases.³²

The gut microbiota is now increasingly acknowledged for its crucial role in hepatocarcinogenesis. We recently reported that the gut microbiota and metabolites contribute to the development and progression of non-alcoholic fatty liver disease (NAFLD)-associated HCC, of which transplanting faeces from NAFLD-HCC mice could induce liver dysplasia with increased inflammation in germ-free mice.³⁴ Using different HCC mouse models, Ma *et al* showed that commensal gut bacteria especially *Clostridium* spp secrete bile acids to increase hepatic CXCR6⁺ NKT cells, thereby strengthening the host antitumour immunity and suppressing tumour progression in the liver.³³ Moreover, another study by Behary *et al* showed that the gut microbiota from patients with NAFLD-HCC induce a T cell immunosuppressive phenotype with decreased CD8⁺ T cells and increased T_{reg}.³⁵ The deficiency of *Akkermansia muciniphila* may induce MDSC infiltration, which promotes liver inflammation, fibrosis and HCC. Taken together, the interplay between gut microbiota and host immune cells plays an important role in NAFLD-HCC progression.

Hepatitis viral infection is another common aetiology of HCC. The gut microbiota in patients with chronic hepatitis B was found to be greatly altered with the significant depletion of beneficial lactic acid bacteria and other probiotics such as *Faecalibacterium prausnitzii*, accompanied with increased serum level of pro-inflammatory cytokine tumour necrosis factor (TNF)-α.³⁶ Meanwhile, excess alcohol consumption can lead to the onset of alcoholic fatty disease (ALD), which may subsequently progress to liver malignancy. The development of ALD-associated HCC is closely related to the gut microbiota, of which gut microbes can metabolise ethanol to produce metabolite acetaldehyde, a compound able to destroy the integrity of intestinal barrier.³⁷ Moreover, similar to viral hepatitis, a marked reduction of gut probiotics including *Lactobacillus* and *Lactococcus* was observed in patients with ALD.³⁸ Hence, the dysbiotic microbiota and increased microbial translocation collectively promote the progression from liver premalignancy to HCC.

Gut microbiota and immune modulation in melanoma

Similar to the gastrointestinal tract, human skin surface is covered by a large number of microbes which also provide a unique milieu for host–microbes interaction. For example, the skin microbiota can communicate with innate immune system to produce antimicrobial molecules as a primary defence against foreign pathogens.³⁹ More specifically, the increased interleukin-17 produced by Th17 protects the host against microbial invasion that passes through the skin.³⁹ Of note, microbiota alteration in the skin can affect the immune system, potentially contributing to melanoma development. On the other hand, various recent studies have demonstrated the association of gut microbiota with the response to melanoma immunotherapy,⁴⁰ suggesting the complex relationship between skin and gut microbes in melanoma. Nevertheless, the mechanism of how gut microbiota modulates immune response during melanoma development needs further investigation.

GUT MICROBIOTA AND IMMUNOTHERAPY EFFICACY

Given the intricate interactions between host immunity and gut microbiota, it is reasonable to propose that microbes can influence immunotherapy efficacy. Immunotherapy is developed to overcome the tolerance towards immune system in tumour cells, thereby restoring a functional antitumour immunity. Three distinct steps are required to allow effective immunotherapy: (1) enhancing antigen presentation of dendritic cells, (2) promoting antitumour T cell responses and (3) vanquishing immunosuppression in the tumour microenvironment.¹⁶ Indeed, the close relationship between microbiota and immunotherapy is now being extensively investigated by a lot of ongoing studies. Here, we focus on research of the capability of microbes to impact immunotherapy.

Immune checkpoint inhibitors

ICIs play an important role in regulating the host immune system. Under normal conditions, these checkpoints help to maintain a balance between co-stimulatory and inhibitory signals of T cell-mediated immunity, thereby ensuring peripheral tolerance and preventing collateral tissue damage caused by overstimulated immune responses against invaded pathogens.⁴¹ However, characteristics of these immunosuppressive checkpoints can be manipulated by tumour cells and used as a means to evade surveillance of antitumour immunity. To restore and improve antitumour immune response, it is plausible to develop therapeutic approaches that aim at suppressing the immune checkpoints. To date, there are multiple monoclonal antibodies approved by the US FDA as ICIs that target the two major negative regulators of immune system, programmed death 1 (PD-1) and its ligand (PD-L1), as well as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4).

PD-1 is a major checkpoint receptor whose expression is upregulated in immune cell lines undergoing programmed cell death.⁴² The ligand PD-L1 is highly expressed in different human cancer types and involved in immune evasion, of which mouse tumour cells with forced PD-L1 expression could not be eliminated by immune response. Monoclonal antibodies against PD-L1 could promote antitumour immune responses, resulting in tumour rejection, hence lays the foundation of anti-PD-1 blockade.⁴³ PD-1 immunosuppressive pathway is initiated by PD-L1/PD-L2 ligation, and its downstream signalling leads to decreased production of pro-inflammatory cytokines and T cell receptor (TCR) inhibition through dephosphorylating intermediates in TCR signalling pathway.⁴³ Taken together, PD-1 pathway causes T cells to become anergic and express an 'exhausted' phenotype.⁴⁴

CTLA-4 is expressed on effector T cells in a regulated fashion while is constitutively expressed on T_{reg}.⁴⁵ CTLA-4 is homologous to CD28, the protein expressed on T cells that provides co-stimulatory signal for T cell activation and proliferation upon interaction with CD80 and CD86 situated on antigen-presenting cells. CTLA-4 has a higher affinity for CD80/CD86 than CD28; hence, it is able to outcompete CD28 for binding, resulting in the disruption of co-stimulatory signal.⁴⁵ Meanwhile, CTLA-4 exerts immunosuppressive function via other mechanisms. The critical role of CTLA-4 in maintaining immune tolerance has been demonstrated, while the efficacy of anti-CTLA-4 is largely dependent on gut microbiota.⁴⁶

Manipulation of microbiota in tumour microenvironment

Increasing evidence has illustrated the presence of microbes within the tumour microenvironment.^{47 48} Tumour growth involves the development of new vasculatures due to the increasing demand for oxygen in rapidly proliferating tumour cells; hence, the tumour microenvironment is widely considered to be necrosis and hypoxia. Such hypoxic condition in the tumour niche could attract the entry of microbes into tumours and

favour their replication.⁴⁹ These approaches mainly aim to facilitate the detection of microbial structural components such as LPS, peptidoglycan, flagellin and other pathogen-associated molecular patterns by innate pattern recognition receptors, subsequently stimulating antitumour immune responses.⁵⁰ Moreover, the antitumour effects of tumour-colonising anaerobic bacteria have been investigated. The presence of bacteria in tumours could cause inflammation which further induces potent immune responses and activates effector CD8⁺ T cells to contribute enhanced tumour immunosurveillance and clearance.⁵¹ Nevertheless, whether approaches that target intratumoral bacteria to promote inflammation are safe and effective in human patients requires further investigations. In contrast, several pathogenic bacteria were found to be enriched in the tumour microenvironment, particularly *F. nucleatum* which is closely linked to colorectal adenocarcinoma.⁵² *F. nucleatum* can inhibit the cytotoxicity of NK cells and antitumour effector T cells, thereby restraining their ability to kill tumour cells.⁵³ In this case, elimination of bacteria, if achievable, should be considered instead to enhance antitumour immune response.

Gut microbiota and immunotherapy response in gastrointestinal cancer

Recent studies have suggested that the gut microbiota is closely related to the efficacy of ICIs in gastrointestinal cancer. For instance, an observational study including 74 patients with different gastrointestinal cancers found that the microbiota composition is significantly different between responders and non-responders of immunotherapy.⁵⁴ In particular, short-chain fatty acid-producing bacteria including *Eubacterium*, *Lactobacillus* and *Streptococcus* were positively associated with ICI response.⁵⁴ Moreover, using CRC mouse models, Mager *et al* identified that *Bifidobacterium pseudolongum* could modulate ICI response through generating the metabolite inosine.¹³

Gut microbiota and immunotherapy response in HCC

The anti-PD-L1 antibody atezolizumab and the vascular endothelial growth factor-neutralising antibody bevacizumab combined therapy has been approved as the first-line therapy for HCC by the FDA, European Medicines Agency and other regulatory agencies.⁵⁵ However, the efficacy of immunotherapy for patients with HCC is largely varied among patients with a response rate of 15%–30%.^{56 57} This suggests that immunotherapy efficacy is dependent on the aetiology of HCC, with diverse hepatic environments distinctly regulating HCC formation and immune response.⁵⁸ Particularly, patients with NAFLD-induced HCC were found to be resistant to ICIs. ICI treatment explicitly increased tumour growth and tumour number in mouse models of NAFLD-HCC induced by choline-deficient high-fat diet. ICIs induce the activation of exhausted CD8⁺ PD1⁺ CXCR6⁺ TNF⁺ T cells, which promote non-alcoholic steatohepatitis-HCC instead of regressing tumour growth.⁵⁵

Gut microbiota and immunotherapy response in melanoma

In the landmark study by Sivan *et al*, mice from two different providers Jackson Laboratory (JAX) or Taconic Farms (TAC), which had distinct microbiota compositions, displayed different rates of subcutaneous melanoma growth of which TAC mice had fewer intratumoral infiltrating CD8⁺ T cells with faster tumour growth than JAX mice.⁵⁹ Through microbial profiling, *Bifidobacterium* was identified to be responsible for a more effective anti-tumour immune system. When combining *Bifidobacterium* administration with PD-L1 blockade, the efficacy of anti-PD-L1 was improved with enhanced dendritic cell maturation as well as their ability to process antigen and produce cytokines.⁵⁹ At the same time, several clinical studies involving patients with melanoma showed the difference in microbiota composition between responders and non-responders receiving anti-PD-1 treatment.^{11 60 61} In responders, the gut microbiota is more diverse with the enrichment of *Faecalibacterium*, in contrast to lower diversity and enriched *Bacteroidales* observed in non-responders.¹¹ Similarly, *B. longum*, *Collinsella aerofaciens* and *Enterococcus faecium* were enriched in responders of patients with metastatic melanoma.⁶⁰ Faecal microbiota transplantation induced the alteration of immune cells and promotes the efficacy of anti-PD-1 therapy in patients with immunotherapy-refractory melanoma.⁶¹ Further mechanistic study showed that the bacterial genus *Enterococcus* improves ICI immunotherapy by producing SAgA.⁶² Together, these findings suggest that altering the gut microbiota by increasing the abundance of several specific microbes could be a potential approach to enhance the efficacy of PD-1 blockade.

CONCLUSION

The gut microbiota plays an important role in regulating immunity and modulating response to cancer therapy. The effect of microbiota in the context of cancer can be either local or systemic depending on different pathological conditions. Here, we present the results of several recent studies, both in experimental animals and in humans, indicating that the gut microbiota can boost the efficacy of immune checkpoint blockade, although the underlying mechanisms still require further investigation. Moreover, it is also increasingly acknowledged that modulation of microbes homing to the intestinal mucosal epithelium or tumour microenvironment may potentially serve as a promising anticancer therapy by itself, or as an adjunct of cancer therapy to improve treatment efficacy. Taken together, the current findings provide solid evidence that modulating the gut microbiota may have important clinical implications, leading us to achieve safer and more efficient treatments for cancers in the future.

Contributors HCHL drafted the review article; XZ revised the manuscript; JY proposed and revised the manuscript.

Funding This project was supported by the National Key R&D Program of China (2020YFA0509200/2020YFA0509203), Shenzhen-Hong Kong-Macao Science and

Technology Program (Category C), Shenzhen (SGDX20210823103535016), RGC-GRF (14117422, 14117123) and the National Natural Science Foundation of China (82103355, 82272619 and 82222901).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- 1 Tsilimigras MCB, Fodor A, Jobin C. Carcinogenesis and therapeutics: the microbiota perspective. *Nat Microbiol* 2017;2:17008.
- 2 Wong SH, Yu J. Gut Microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nat Rev Gastroenterol Hepatol* 2019;16:690–704.
- 3 Yu J, Feng Q, Wong SH, *et al*. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut* 2017;66:70–8.
- 4 Rothschild D, Weissbrod O, Barkan E, *et al*. Environment dominates over host genetics in shaping human gut Microbiota. *Nature* 2018;555:210–5.
- 5 Durack J, Lynch SV. The gut microbiome: relationships with disease and opportunities for therapy. *J Exp Med* 2019;216:20–40.
- 6 Cheng WY, Wu CY, Yu J. The role of gut microbiota in cancer treatment: friend or foe. *Gut* 2020;69:1867–76.
- 7 Yachida S, Mizutani S, Shiroma H, *et al*. Metagenomic and metabolomic analyses reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer. *Nat Med* 2019;25:968–76.
- 8 Helmink BA, Khan MAW, Hermann A, *et al*. The microbiome, cancer, and cancer therapy. *Nat Med* 2019;25:377–88.
- 9 Chilakapati SR, Ricciuti J, Zsiris E. Microbiome and cancer immunotherapy. *Curr Opin Biotechnol* 2020;65:114–7.
- 10 Levy M, Kolodziejczyk AA, Thaïs CA, *et al*. Dysbiosis and the immune system. *Nat Rev Immunol* 2017;17:219–32.
- 11 Gopalakrishnan V, Spencer CN, Nezi L, *et al*. Gut Microbiome modulates response to anti-PD-1 immunotherapy in Melanoma patients. *Science* 2018;359:97–103.
- 12 Huang C, Li M, Liu B, *et al*. Relating gut Microbiome and its Modulating factors to Immunotherapy in solid tumors: a systematic review. *Front Oncol* 2021;11:642110.
- 13 Mager LF, Burkhard R, Pett N, *et al*. Microbiome-derived Inosine modulates response to checkpoint inhibitor Immunotherapy. *Science* 2020;369:1481–9.
- 14 Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes* 2012;3:4–14.
- 15 Marigo I, Dolcetti L, Serafini P, *et al*. Tumor-induced tolerance and immune suppression by myeloid derived suppressor cells. *Immunol Rev* 2008;222:162–79.
- 16 Mittal D, Gubin MM, Schreiber RD, *et al*. New insights into cancer immunoediting and its three component phases—elimination, equilibrium and escape. *Curr Opin Immunol* 2014;27:16–25.
- 17 Choudhry H. The microbiome and its implications in cancer immunotherapy. *Molecules* 2021;26:206.
- 18 Diamond MS, Kinder M, Matsushita H, *et al*. Type I interferon is selectively required by dendritic cells for immune rejection of tumors. *J Exp Med* 2011;208:1989–2003.
- 19 Teng MWL, Vesely MD, Duret H, *et al*. Opposing roles for IL-23 and IL-12 in maintaining occult cancer in an equilibrium state. *Cancer Res* 2012;72:3987–96.
- 20 Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature* 2011;480:480–9.
- 21 Fu Y, Liu S, Zeng S, *et al*. From bench to bed: the tumor immune microenvironment and current immunotherapeutic strategies for hepatocellular carcinoma. *J Exp Clin Cancer Res* 2019;38:396.
- 22 Ma J, Huang L, Hu D, *et al*. The role of the tumor microbe microenvironment in the tumor immune microenvironment: bystander, activator. *J Exp Clin Cancer Res* 2021;40:327.

- 23 Li X, Liu R, Su X, *et al.* Harnessing tumor-associated macrophages as AIDS for cancer immunotherapy. *Mol Cancer* 2019;18:177.
- 24 Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol* 2009;9:162–74.
- 25 Wong SH, Zhao L, Zhang X, *et al.* Gavage of fecal samples from patients with colorectal cancer promotes intestinal carcinogenesis in germ-free and conventional mice. *Gastroenterology* 2017;153:1621–33.
- 26 Ivanov II, Atarashi K, Manel N, *et al.* Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell* 2009;139:485–98.
- 27 Kostic AD, Chun E, Robertson L, *et al.* *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe* 2013;14:207–15.
- 28 Wu J, Li Q, Fu X. *Fusobacterium nucleatum* contributes to the carcinogenesis of colorectal cancer by inducing inflammation and suppressing host immunity. *Transl Oncol* 2019;12:846–51.
- 29 Tsoi H, Chu ESH, Zhang X, *et al.* *Peptostreptococcus anaerobius* induces intracellular cholesterol biosynthesis in colon cells to induce proliferation and causes dysplasia in mice. *Gastroenterology* 2017;152:1419–33.
- 30 Long X, Wong CC, Tong L, *et al.* *Peptostreptococcus anaerobius* promotes colorectal carcinogenesis and modulates tumour immunity. *Nat Microbiol* 2019;4:2319–30.
- 31 Zhao L, Zhang X, Zhou Y, *et al.* *Parvimonas micra* promotes colorectal tumorigenesis and is associated with prognosis of colorectal cancer patients. *Oncogene* 2022;41:4200–10.
- 32 Tripathi A, Debelius J, Brenner DA, *et al.* The gut-liver axis and the intersection with the microbiome. *Nat Rev Gastroenterol Hepatol* 2018;15:785.
- 33 Ma C, Han M, Heinrich B, *et al.* Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science* 2018;360:eaan5931.
- 34 Zhang X, Coker OO, Chu ES, *et al.* Dietary cholesterol drives fatty liver-associated liver cancer by modulating gut microbiota and metabolites. *Gut* 2021;70:761–74.
- 35 Behary J, Amorim N, Jiang X-T, *et al.* Gut Microbiota impact on the peripheral immune response in non-alcoholic fatty liver disease related hepatocellular carcinoma. *Nat Commun* 2021;12:187.
- 36 Lu H, Wu Z, Xu W, *et al.* Intestinal Microbiota was assessed in cirrhotic patients with hepatitis B virus infection. Intestinal microbiota of HBV cirrhotic patients. *Microb Ecol* 2011;61:693–703.
- 37 Elamin EE, Masclee AA, Dekker J, *et al.* Ethanol metabolism and its effects on the intestinal epithelial barrier. *Nutr Rev* 2013;71:483–99.
- 38 Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. *Gastroenterology* 2014;146:1513–24.
- 39 Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. *Science* 2014;346:954–9.
- 40 Mekadim C, Skalikova HK, Cizkova J, *et al.* Dysbiosis of skin microbiome and gut microbiome in melanoma progression. *BMC Microbiol* 2022;22:63.
- 41 Pardoll DM. The blockade of immune checkpoints in cancer Immunotherapy. *Nat Rev Cancer* 2012;12:252–64.
- 42 Ishida Y, Agata Y, Shibahara K, *et al.* Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J* 1992;11:3887–95.
- 43 Keir ME, Butte MJ, Freeman GJ, *et al.* PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol* 2008;26:677–704.
- 44 Chinai JM, Janakiram M, Chen F, *et al.* New immunotherapies targeting the PD-1 pathway. *Trends Pharmacol Sci* 2015;36:587–95.
- 45 Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol* 2016;39:98–106.
- 46 Vétizou M, Pitt JM, Daillère R, *et al.* Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 2015;350:1079–84.
- 47 Nejman D, Livyatan I, Fuks G, *et al.* The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science* 2020;368:973–80.
- 48 Liu W, Zhang X, Xu H, *et al.* Microbial community heterogeneity within colorectal neoplasia and its correlation with colorectal carcinogenesis. *Gastroenterology* 2016;120:2395–408.
- 49 Wouters BG, Koritzinsky M, Chiu RK, *et al.* Modulation of cell death in the tumor microenvironment. *Semin Radiat Oncol* 2003;13:31–41.
- 50 Ranf S. Immune sensing of lipopolysaccharide in plants and animals: same but different. *PLoS Pathog* 2016;12:e1005596.
- 51 Bashiardes S, Tuganbaev T, Federici S, *et al.* The microbiome in anti-cancer therapy. *Semin Immunol* 2017;32:74–81.
- 52 Rubinstein MR, Wang X, Liu W, *et al.* *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-Cadherin/ beta-Catenin signaling via its FADA Adhesin. *Cell Host Microbe* 2013;14:195–206.
- 53 Gur C, Ibrahim Y, Isaacson B, *et al.* Binding of the Fap2 protein of *fusobacterium nucleatum* to human inhibitory receptor TIGIT protects tumors from immune cell attack. *Immunity* 2015;42:344–55.
- 54 Peng Z, Cheng S, Kou Y, *et al.* The gut microbiome is associated with clinical response to anti-PD-1/PD-L1 immunotherapy in gastrointestinal cancer. *Cancer Immunol Res* 2020;8:1251–61.
- 55 Sangro B, Sarobe P, Hervás-Stubbs S, *et al.* Advances in immunotherapy for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2021;18:525–43.
- 56 Duffy AG, Ulahannan SV, Makorova-Rusher O, *et al.* Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol* 2017;66:545–51.
- 57 Finn RS, Qin S, Ikeda M, *et al.* Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;382:1894–905.
- 58 Roderburg C, Wree A, Demir M, *et al.* The role of the innate immune system in the development and treatment of hepatocellular carcinoma. *Hepat Oncol* 2020;7:HEP17.
- 59 Sivan A, Corrales L, Hubert N, *et al.* Commensal bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 2015;350:1084–9.
- 60 Matson V, Fessler J, Bao R, *et al.* The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018;359:104–8.
- 61 Baruch EN, Youngster I, Ben-Betzalel G, *et al.* Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021;371:602–9.
- 62 Griffin ME, Espinosa J, Becker JL, *et al.* Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy. *Science* 2021;373:1040–6.