Received: 18 April 2021 | Accepted: 20 July 2021

DOI: 10.1111/imm.13397

Immunology
The Journal of cells, molecules, systems and technologies
British Society for immunology

REVIEW

Interaction between intestinal microbiota and tumour immunity in the tumour microenvironment

Xiuxiu Yang[1,2,3] | **Yaxin Guo**[3,4,5] | **Chen Chen**[3,6] | **Bo Shao**[1,3] | **Luyang Zhao**[3,4,5] | **Quanbo Zhou**[1] | **Jinbo Liu**[1] | **Guixian Wang**[1] | **Weitang Yuan**[1] | **Zhenqiang Sun**[1,3]

[1]Department of Colorectal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

[2]School of Medicine, Zhengzhou University, Zhengzhou, China

[3]Academy of Medical Sciences, Zhengzhou University, Zhengzhou, China

[4]Department of Basic Medical, Academy of Medical Sciences of Zhengzhou University, Zhengzhou, China

[5]Henan Academy of Medical and Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, China

[6]School of Life Sciences, Zhengzhou University, Zhengzhou, China

Correspondence
Weitang Yuan and Zhenqiang Sun, Department of Colorectal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China.
Emails: yuanweitang@zzu.edu.cn; fccsunzq@zzu.edu.cn

Senior author: Zhenqiang Sun

Funding information
This study was supported by The National Natural Science Foundation of China (81972663, 81560385), Key Scientific Research Projects of Institutions of Higher Education in Henan Province (19A310024), The Medical Scientific and Technological Research Project of Henan Province

Abstract

In recent years, an increasing number of studies have reported that intestinal microbiota have an important effect on tumour immunity by affecting the tumour microenvironment (TME). The intestinal microbiota are closely associated with various immune cells, such as T lymphocytes, natural killer cells (NK cells) and macrophages. Some bacteria, such as *Akkermansia muciniphila (A. muciniphila)* and *Lactobacillus reuteri (L. reuteri)*, have been shown to improve the effect of tumour immunity. Furthermore, microbial imbalance, such as the increased abundance of *Fusobacterium nucleatum (F. nucleatum)* and *Helicobacter hepaticus (H. hepaticus)*, generally causes tumour formation and progression. In addition, some microbiota also play important roles in tumour immunotherapy, especially PD-L1-related therapies. Therefore, what is the relationship between these processes and how do they affect each other? In this review, we summarize the interactions and corresponding mechanisms among the intestinal microbiota, immune system and TME to facilitate the research and development of new targeted drugs and provide new approaches to tumour therapy.

Abbreviations: 4-HNE, netrin-1 and trans-4-hydroxy-2-nonenal; *A. muciniphila*, *Akkermansia muciniphila*; APC, antigen-presenting cells; *B. subtilis*, *Bacillus subtilis*; BSE, bystander effect; *C. butyricum*, *Clostridium butyricum*; CAFs, cancer-associated fibroblasts; cDCs, conventional dendritic cells; CDDL, long subtype of the bacterial enzyme cytidine deaminase; CECs, colonic epithelial cells; CIN, initiate chromosomal instability; COX-2, cyclooxygenase-2; CSCs, colorectal cancer stem cells; CTSK, cathepsin K; DC, dendritic cells; Dclk1, doublecortin-like kinase 1; *E. faecalis*, *Enterococcus faecalis*; ELC, encapsulated liposomal clodronate; EMT, epithelial–mesenchymal transition; ETBF, enterotoxic *Bacteroides fragilis*; ETEC, enterotoxigenic *Escherichia coli*; *F. nucleatum*, *Fusobacterium nucleatum*; GALT, gut-associated lymphoid tissue; GF, germ free; GPR, G protein-coupled receptor; *H. hepaticus*, *Helicobacter hepaticus*; ICB, immune checkpoint blocking; ICIs, immune checkpoint inhibitors; IEC, intestinal epithelial cells; IFN, interferons; *L. reuteri*, *Lactobacillus reuteri*; *Lp*, *Lactobacillus plantarum*; LPS, lipopolysaccharide; MALT, mucosa-associated lymphoid tissue; MD, muramyl dipeptide; MDSCs, myeloid-derived suppressor cells; mesoDAP, diaminopimelic acid; MMP-9, matrix metalloproteinase-9; NK cells, natural killer cells; pDCs, plasmacytoid dendritic cells; PGLYRP3, peptidoglycan recognition protein 3; PPs, Peyer's patches; PSA, polysaccharides; PSK, protein-bound polysaccharide; SCFA, short-chain fatty acids; TAMs, tumour-associated macrophages; TILs, tumour-infiltrating lymphocytes; TLR4, Toll-like receptor 4; TME, tumour microenvironment; TNF-α, tumour necrosis factor-α; Treg, regulatory T cells; UPR, unfolded protein response; VEGF, vascular endothelial growth factor; Wif1, Wnt inhibitor factor 1.

(201702027), Youth Innovation Fund Project of The First Affiliated Hospital of Zhengzhou University (YNQN2017035), The China Postdoctoral Science Foundation (2019T120648, 2017M610462), The National Natural Science Foundation of Henan Province (182300410342) and The Health Commission Technology Talents Overseas Training Project of Henan Province (2018140).

KEYWORDS

immune, intestinal microbiota, tumour microenvironment, tumour therapy

INTRODUCTION

Composition and function of intestinal microecology

Intestinal microecology refers to a relatively stable ecosystem formed by the interaction between microbiota colonizing the human intestine and the human body. Under the rise of immunotherapy and next-generation sequencing, the microbiome has recently emerged as a promising frontier in TME. It is estimated that there are 10–100 trillion bacteria containing approximately 500–1500 different bacterial species existing in the human gastrointestinal tract [1]. As the largest and most complex ecosystem of the human body, gut microbiota and thousands of their metabolites influence almost every aspect of host physiological activities. The core functions of mature and healthy gut microbiota include the following: genes encoding glycosaminoglycan degradation [2], short-chain fatty acids (SCFA) produced by fermenting complex polysaccharides and synthesizing special lipopolysaccharides [3], synthesis of some essential amino acids [4] and vitamins [5], etc. Gut microbiota is closely related to maintaining immunity. A study found that introducing *L. reuteri* into sterile mice boosted the production of immune cells [6]. However, the use of antibiotics can cause imbalances in the gut microbiota, which trigger immune disorders [7]. As a result, the imbalance of gut microbiota leads to many diseases and even tumours. Changes in local microbiota composition and deficiency in tumour immune surveillance may lead to tumour development [8]. The intestinal microbiota also regulate drug sensitivity by metabolism [9–11].

Composition and function of tumour microenvironment (TME)

TME is composed of different types of cells, such as endothelial cells, fibroblasts, tumour-associated macrophages, regulatory T cells (Treg), myeloid-derived suppressor cells (MDSCs) and cancer-associated fibroblasts (CAFs). Extracellular components, including cytokines, growth factors, hormones and extracellular matrix, are also included in TME. They exist around tumour cells and are nourished by the vascular network. Increasing reports show that microorganism is also an important part of TME in some tumours [12,13].

Tumour growth depends not only on genetic mutation but also on changes in the TME, such as the stroma, blood vessels and immunocytes. TME promotes tumour development by inducing angiogenesis [14,15], activating invasion and metastasis [16,17], evading the immune system [18,19], and reshaping energy metabolism [20,21]. Immunity and inflammation are at the core of TME [22,23]. Therefore, this article will focus on commensal bacteria in TME. In recent years, an increasing number of scientists have begun to focus their treatment strategies on the tumour immunity to regulate the immune environment of tumour cells. Immune checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 represent milestones in the research of TME immune therapy [24–26]. The intestinal microbiota are involved in immune regulation and promote the immune response. Intestinal microbiota' disorders promote tumour formation [27–29]. Intestinal microbiota, as important participants in the intestinal environment, have a certain relationship with the tumour immune response [30–32]. Therefore, intestinal microbiota imbalance may influence tumour development by reshaping the TME and changing the immune response.

INTESTINAL MICROBIOTA AND THE IMMUNE SYSTEM

Intestinal microbiota and the immune barrier

The intestinal immune barrier mainly includes mucosa-associated lymphoid tissue (MALT) and intestinal commensal microbiota. MALT is the main component of the mucosal immune system, including gut-associated lymphoid tissue (GALT). Studies have shown that oral PSK, a protein-bound polysaccharide derived from *Basidiomycetes*, improves the damaged antitumour CD4+ T-cell response in the GALT by inhibiting the production

of TGF-β and IFN-γ in mouse models [33,34]. GALT includes Peyer's patches (PPs) located in the small intestine wall and solitary lymphoid follicles scattered throughout the intestine. PPs are an extremely important part of the intestinal immunity, which is made up of lymphocytes [35]. In addition, intestinal commensal microbiota can assist in nutrient uptake and metabolism and toxin degradation [36,37]. The epithelial tissue barrier can be maintained to prevent the invasion of pathogenic bacteria. It also ensures the stability of the intestinal microecology by competing with pathogenic bacteria for space and nutrients, producing antimicrobial substances and inhibiting the inflammatory response of epithelial tissues [38]. Moreover, intestinal commensal microbiota regulate immune cell differentiation [39,40].

The intestinal mucus layer, epithelial layer and GALT provide an important internal environment and a place of attachment for the intestinal microecology. Intestinal microbiota promote the development and maturation of the intestinal mucosa. These two are interdependent and maintain the stability of the intestinal mucosal barrier.

Intestinal microbiota and immune response

Gut microbiota interacts with immune response, mainly through the antigenicity of its own components and metabolites produced by breaking down nutrients in food. Lipopolysaccharide (LPS) is a component of the cell wall of gram-negative bacteria in the intestine. LPS stimulates small intestinal epithelial cells (IEC) through the cell-surface TLR pathway to cause phosphorylation of IRAK and MAP, increase IL-8 expression and cause the body immune response [41]. In addition, LPS induces phosphorylation of myosin light chain kinase, thereby enhancing the permeability of the intestinal mucosal barrier, which is one of the mechanisms that trigger sepsis (Figure 1a) [42]. As the main component of bacterial cell wall, peptidoglycan exists in gram-negative bacteria and gram-positive bacteria. Studies have shown that peptidoglycan in the intestinal microbiota mainly affects the innate immune system through NOD1/NOD2. Muramyl dipeptide (MDP) is one of the structures of gram-positive bacterial peptidoglycan. MDP promotes the survival of Lgr5+ stem

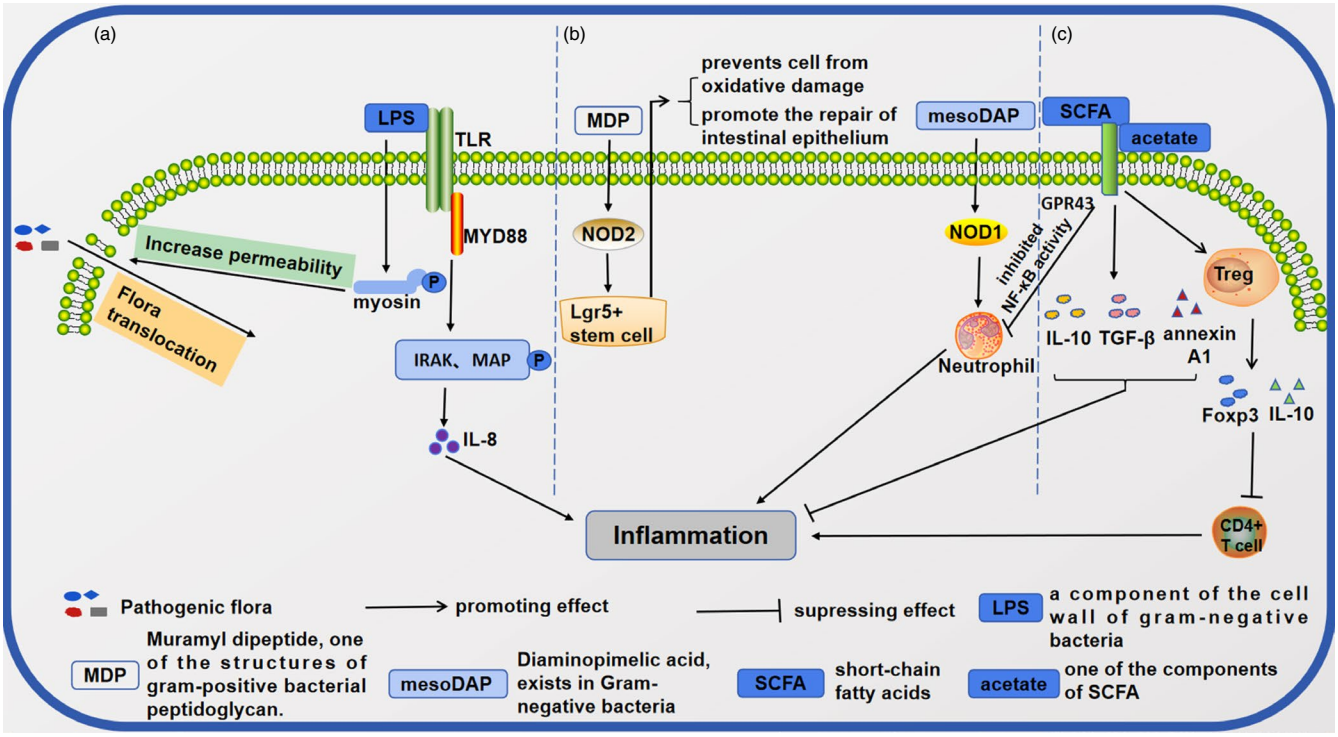

FIGURE 1 Interconnections among gut microbial cells, their metabolites and body immunity. (a) LPS promotes inflammation through TLR-MYD88-phosphorylation signalling pathways. (b) MDP promotes the survival of Lgr5+ stem cells in intestinal crypts through NOD2 and prevents them from damage, thereby promoting the repair of intestinal epithelium. mesoDAP enhances the lethality of bone marrow-derived neutrophils through NOD, promoting inflammation. (c) SCFA acts on Treg cells through GPR43, improve the number of Treg cells and upregulate gene expression of Foxp3 and IL-10 in Treg cells, which in turn inhibits the effector CD4+ T cells and relieves colitis. As one of the components of SCFA, acetate reduces inflammation by inhibiting NF-κB activity of neutrophil and promoting the secretion of anti-inflammatory factors IL-10, TGF-β and annexin A1

cells in intestinal crypts through NOD2 and prevents them from oxidative damage, thereby promoting the repair of intestinal epithelium [43]. Peptidoglycan recognition protein 3 (PGLYRP3) and NOD2 can alleviate ulcerative colitis in mice [44]. Diaminopimelic acid (mesoDAP) in gram-negative bacteria enhances the lethality of bone marrow-derived neutrophils stimulated by *Streptococcus pneumoniae* and *Staphylococcus aureus* through NOD1. The concentration of peptidoglycan in serum is related to neutrophil function. In vivo administration of NOD1 ligand is sufficient to restore neutrophil function after the microbiota is depleted (Figure 1b) [45]. It is reported that SCFA acts on Treg cells in the intestine through the G protein-coupled receptor (GPR)43, increases the number of Treg in the intestine caused by vancomycin and upregulates gene expression of Foxp3 and IL-10 in Treg cells in sterile mouse, which in turn inhibits the effector CD4+ T cells and relieves colitis [46]. As one of the components of SCFA, acetate reduces inflammation by inhibiting NF-κB activity of neutrophil and promoting the secretion of anti-inflammatory factors IL-10, TGF-β and annexin A1 (Figure 1c) [47]. In addition, as a bacterial metabolite, polysaccharide (PSA) is recognized by dendritic cells (DC) in the small intestine and activate CD4+ T cells to secrete cytokines, thereby promoting T-cell proliferation in sterile mice, improving TH1/TH2 cell disorders and promoting lymph organization formation [48].

Therefore, gut microbiota is very important for the formation and maintenance of innate immunity under physiological conditions and the changes of body immunity under inflammatory conditions. Regulating the intestinal microecology and restoring immune function are key to the treatment of immune diseases [49] and might also be a new direction for future tumour treatment.

Intestinal microbiota and antitumour immune responses

There is a dynamic and balanced network of interactions between gut microbiota and human immune cells. Recent studies have found that intestinal microbiota can affect antitumour immunity, and the efficacy of immune checkpoint blocking (ICB) therapy may depend on specific intestinal bacteria. However, the underlying mechanism by which the microbiome enhances antitumour immunity remains unclear. Recent studies have shown that the intestinal *Bifidobacterium pseudolongum* can enhance the response of immunotherapy by producing the metabolite inosine. Immunotherapy will induce a decrease in the intestinal barrier function and increase the systemic transport of inosine and activated antitumour T cells. The role of inosine depends on the expression of adenosine A2A receptor (A2AR) in T cells. Interestingly, previous studies have shown that inosine can bind to A2AR and can inhibit Th1 differentiation in vitro and antitumour immunity in vivo. The Th1 promotion effect of inosine depends on the A2AR signal in T cells, and the inosine-A2AR-cAMP-PKA signal cascade leads to the enhanced transcription of the key factors of Th1 differentiation (IL-12 receptor and IFN-γ). However, the effect of inosine on T cells requires sufficient co-stimulation to enable IL-12 receptors to participate in Th1 differentiation and produce IFN-γ to achieve effective antitumour immunity [50]. Another study showed that *Bifidobacteria* not only accumulate in the intestine, but also migrate to tumour tissues, activating the interferon gene stimulating factor (STING) immune signalling pathway in DC cells and re-exposing the tumour to the attack of the acquired immune system. In addition, after genetic modification, mice with type 1 interferon deletion or STING pathway blocked cannot benefit from bacterial immunotherapy, indicating that the STING signalling pathway plays a vital role in CD47 antibody therapy [51]. Besides, scientists have identified a 'cocktail' therapy containing 11 strains, which activates the immune system and delay the growth of melanoma in mice. Unfolded protein response (UPR) is a cell signalling pathway that maintains protein homeostasis. A decrease in UPR is observed in melanoma patients who responded to immune checkpoint therapy. RNF5 is a ubiquitin ligase that helps remove improperly folded or damaged proteins. When mice lacking RNF5 have a complete immune system and intestinal microbiome, the growth of melanoma is also inhibited. Using an antibiotic cocktail to act on mice, or feeding them with common wild companions, the antitumour immunity phenotype disappeared, and tumour rejection was eliminated. This indicates the important role of the gut microbiome in antitumour immunity [51].

In short, there are relatively few studies on the molecular mechanism of intestinal microbiota and antitumour immunity. However, existing studies can predict that the intestinal microbiota and its metabolites interact with tumours through immune-related molecule and checkpoint mechanisms.

INTESTINAL MICROBIOTA AND IMMUNITY IN THE TME

Role of immune cells induced by intestinal microbiota in the TME

Macrophages

On the one hand, specific intestinal microorganisms affect tumorigenesis and development through tumour-associated

macrophages (TAMs) in the TME. Mammary tumours in *H. hepaticus*-infected $Rag2^{-/-}Apc^{Min/+}$mice have dense infiltrates of macrophages [52]. On the other hand, the disorder of microbiota in the intestinal tract also promotes tumour development. Wan et al. demonstrated that intestinal dysbacteriosis leads to TAM activation, subsequently promoting the secretion of IL-6 and TNF-α. The increased expression of N-cadherin and vimentin and decreased expression of E-cadherin contribute to epithelial-mesenchymal transition (EMT). All of these factors boost the development of CRC [53]. Some microbiota stimulate macrophages to increase c-Jun phosphorylation in CRC cells, accordingly accelerating CRC cell proliferation [54]. Dysbacteriosis induced by vancomycin causes hyperplasia of colonic epithelial tuft cells and promotes the production of IL-25 derived from tuft cells. Subsequently, IL-25 promotes EMT and the migration of HCC cells by alternatively activating M2 macrophages in the TME and promoting the secretion of CXCL10. CXCL10 promotes the infiltration of CD8+ T cells in the TME and facilitates tumour development [55]. The intestinal microbiota plays an important role in the metastasis of CRC as an important regulator of the intestinal microenvironment. Cathepsin K (CTSK) is a secreted protein associated with metastasis. CTSK produces intestinal microbe imbalances and the metastasis of CRC. Interestingly, CTSK, secreted by tumour cells bound to Toll-like receptor 4 (TLR4) through mTOR-dependent pathways, activates TAMs. Furthermore, CTSK stimulates TAMs to secrete IL-10 and IL-17, promoting the invasion and metastasis of CRC cells through the NF-κB pathway. In clinical terms, the high expression of CTSK in tumour tissues is closely associated with CRC metastasis and poor prognosis [56]. Therefore, TAMs in the TME play an active role in tumorigenesis, including initiation and progression (Figure 2a). Moreover, the cytokines produced during this process have the potential to be used clinically as biomarker.

Neutrophils

The cytoplasm of neutrophils contains azurophilic granules and special granules. The former is lysosomes containing acid phosphatase, myeloperoxidase and various acidic hydrolases, which digest phagocytosed bacteria and foreign objects. The special granules are secretory granules containing lysozyme and defensin, which have bactericidal activity. Neutrophils have strong chemotactic and phagocytic functions, and they mainly swallow bacteria [57–59]. Neutrophils are closely associated with tumour development in the TME [60,61]. One recent study reported that *H. hepaticus* in the intestine promotes tumour formation often through neutrophils. *H. hepaticus* requires neutrophils to promote mammary tumorigenesis, and this phenomenon can be reversed by treating mice with an anti-Ly6G antibody. Ly6G is a marker of mature neutrophils [62]. A similar experiment showed the effect of *H. hepaticus* on colorectal carcinogenesis. $Rag2^{-/-}$ mice infected with *H. hepaticus* produce Gr-1(+) neutrophils. Neutrophils increase the levels of NO and TNF-α, thereby activating the NF-κB signalling pathway, leading to tumorigenesis [63]. Thus, *H. hepaticus* promotes intestinal and extra-intestinal tumours through neutrophils in the TME (Figure 2b). As research progresses, treating certain tumours by affecting neutrophils may also become a promising strategy.

Myeloid-derived suppressor cells (MDSCs)

MDSCs is a group of cells composed of granulocytes, mononuclear macrophages and myeloid precursor cells in the early differentiation stage, with heterogeneity and differentiation potential. MDSCs induced by intestinal microbiota usually play an immunosuppressive role in the TME [31,64].

IL-17 recruits bone MDSCs into the colon TME of mice colonized with enterotoxic *Bacteroides fragilis* (ETBF). ETBF indirectly induces the ectopic production of chemokines and growth factors by colonic epithelial cells (CECs) through direct interaction with IL-17 receptors. ETBF also induces submucosal IL-17 expression. IL-17 and transformed CECs jointly promote tumour development by suppressing immune effector cells and activating the STAT3 signalling pathway, together with pro-angiogenic mediators, that is, matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF) [65]. *F. nucleatum* also has the potential to promote intestinal tumorigenesis by increasing MDSC populations, including monocytes (M-MDSCs) and granulocytes (G-MDSCs), in the TME. In addition, M-MDSCs express higher levels of arginase-1 and iNOS than G-MDSCs. As a result, MDSCs show significant T-cell suppression activity, leading to tumorigenesis [66]. The lack of microbiota in early life in mice enhances the expression of CXCR2 ligands, which recruit G-MDSCs in the colonic TME. Interestingly, the activity of MDSC-driven colonic tumorigenesis is inhibited by early-life microbe exposure [67]. Consequently, certain intestinal pathogenic microorganisms or abnormal intestinal microecology and synergistic interactions with cytokines activate and proliferate MDSCs in the TME to mediate the immune escape of tumour cells (Figure 2e).

T cells

T cells mediate the adaptive cellular immune response and play an important auxiliary role in the thymus-dependent

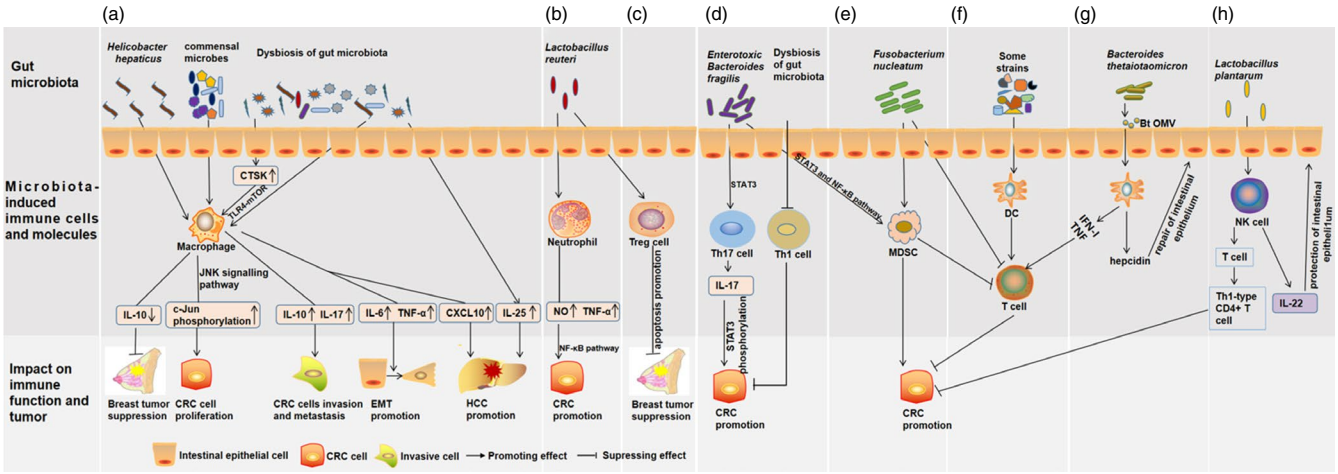

FIGURE 2 Microorganisms promote or inhibit tumorigenesis by affecting different immunocytes in the TME. (a) *Helicobacter hepaticus* activates macrophages. Macrophages inhibit the production of IL-10, which inhibits the development of breast tumours. Some commensal microbiota stimulate macrophages to increase c-Jun phosphorylation in CRC cells via the JNK signalling pathway, accelerating CRC cell proliferation. Intestinal microbiota dysbacteriosis induces tumour cells to secrete CTSK, thereby activating macrophages via mTOR-dependent pathways. CTSK stimulates macrophages to secrete IL-10 and IL-17, promoting the invasion and metastasis of CRC cells. Intestinal flora dysbacteriosis directly activates macrophages. Macrophages release IL-6, TNF-α and CXCL10. IL-6 and TNF-α accelerate the development of CRC by promoting EMT. CXCL10 induces the infiltration of T cells in the TME and promotes HCC development. Intestinal microbiota dysbacteriosis also induces the production of IL-25 derived from tuft cells. IL-25 promotes EMT and the migration of HCC cells. (b) *Helicobacter hepaticus* activates neutrophils. Neutrophils increase the levels of NO and TNF-α, activate the NF-κB signalling pathway and lead to CRC. (c) *Lactobacillus reuteri* stimulates Treg cells. Treg cells inhibit the development of breast tumours by promoting apoptosis. (d) Enterotoxic *Bacteroides fragilis* can also activate Th17 cells through the STAT3 signalling pathway. Th17 cells release IL-17 cytokines. IL-17 promotes STAT3 phosphorylation in the colorectal epithelium and tumour cells, thereby promoting tumorigenesis. (e) EBTF activates MDSCs through the STAT3 and NF-κB signalling pathways, directly promoting tumorigenesis. *Fusobacterium nucleatum* increases MDSC populations. MDSCs show significant T-cell suppression activity, leading to tumorigenesis. (f) *F. nucleatum* suppresses T cells indirectly through MDSCs. *F. nucleatum* also directly inhibits T cells. T cells play a role in inhibiting tumour development in the TME. Some strains activate T cells through DCs in the TME to inhibit the growth of CRC. (g) DCs secrete IFN and TNF to initiate T-cell activation. Hepcidin can repair the intestinal mucosa. (h) *Lactobacillus plantarum*-induced NK cells enhance IL-22 production. IL-22 provides protection of the intestinal epithelial barrier. NK cells promote T-cell differentiation, enhancing the antitumour immune response and delay tumour formation

antigen-induced humoral immune response. T-cell defects affect the cellular immune response and humoral immune response, which may lead to susceptibility to a variety of pathogenic microorganisms and even opportunistic pathogenic microorganisms (such as *Candida albicans* and *Pneumocystis carinii*) [68,69]. Abnormality or lack of T cells in TME will reduce the antitumour effect and cause certain pathological phenomena [32].

The integrity of the intestinal microbiota is pivotal to induce antitumour activity in vivo [70]. Therefore, intestinal microorganisms activate immune cells in the TME and thus exert various antitumour effects. Some studies have shown that the presence of certain microbiota in the TME contributes to the antitumour effect. Tanoue et al. reported that a commensal consortium activates CD8 T cells without causing inflammation. There are 11 strains that enhance the expression of MHC class I in DCs, which subsequently activate IFN-γ+ CD8 T cells, increasing the number of IFN-γ+ CD8 tumour-infiltrating lymphocytes (TILs) in the TME to inhibit the growth of CRC [71]. The general process is that after abnormal intestinal microorganisms invade the body, CD8 T cells differentiate into CTL under the help of antigen-presenting cells, IL-2 and IL-6. And CTL produce IFN-γ, TNF-α, FASL and so on to play a killing effect on tumour cells. However, other studies have reported that the presence of certain microbiota in the TME is not conducive to exerting antitumour effects. For example, the amount of *F. nucleatum* is inversely associated with the density of CD3+ T cells, which have an antitumour effect in colonic tumour patients [72]. Therefore, the presence of different microorganisms in the intestine has the opposite effect on the tumour by affecting T cells in the TME (Figure 2f).

Treg cells

Treg cells negatively regulate the immune response in two ways: (1) through directly contacting and inhibiting the activation of target cells and (2) secreting TGF-β, IL-10 and other cytokines to inhibit the immune response. Tregs play an important role in many processes and

diseases, such as immune tolerance, autoimmune diseases, infectious diseases [73–75], organ transplantation and the TME [76–78]. A study showed that Treg cells that interact with *H. hepaticus* effectively suppress tumorigenesis in mouse models regardless of their tumour aetiology. *H. hepaticus* infection leads to increased expression levels of TNF-α, which is pivotal in tumour formation in the gut mucosa. However, early contact with *H. hepaticus* results in a reduced amount of TNF-α. This difference is not beneficial to subsequent tumorigenesis [52]. TNF-α and IL-1β are both very important in inducing inflammation and leading to tumour development via the NF-κB signalling pathway [79]. Treg cells can also be recruited by *L. reuteri* in the TME. Eating a Western 'fast food' diet induced precancerous lesion formation in hybrid Swiss mice, leading to breast cancer. The TME was characterized by an increase in the mast cell population and a decrease in the Treg cell population. Tumour characteristics induced by the Western diet were significantly reduced after the administration of *L. reuteri*. Further studies showed that the antitumour effects of *L. reuteri* require the involvement of Treg cells. Mice with HER2 gene mutations are susceptible to breast cancer. After *L. reuteri* was given to these mice, the tumour-free survival rate increased. The underlying mechanism involved *L. reuteri* inducing an increase in the Treg cell population, leading to increased apoptosis in breast tissue, thus playing an antitumour role [80]. From the above results, it can be concluded that the interaction between certain microorganisms and Tregs in the TME often has an antitumour effect (Figure 2c). This suggests that the use of treatments targeting the regulation of Treg cells may be a new breakthrough point for the treatment of tumours.

Th cells

All Th cells express the immune molecule CD4, and they influence humoral and cellular immunity by secreting different types of cytokines [81,82]. Cytokines produced by different types of Th cells in the TME have different effects on the development of tumours [83,84]. Thus, it is necessary to study how the intestinal microecology effects Th cells in the TME. The response of Th17 cells is earlier than that of other T cells, and Th17 cells can accumulate in the intestine, which indicates that the development of Th17 cells is regulated by the intestinal mechanism. In agreement with this, the number of Th17 cells in the intestines dropped sharply in mice treated with antibiotics or sterile mice. Therefore, intestinal microorganisms play an important role in regulating the proliferation and differentiation of Th17 cells. TH17 cells mainly secrete IL-17A, IL-17F and IL-22. After IL-17 binds to the receptor, it activates the activity of NF-κB by activating MAP kinase, thereby exerting the biological activity of IL-17. IL-17A is a pro-inflammatory cytokine that can recruit neutrophils and promote the production of inflammatory factors, chemokines such as IL-6, IL-8, MCP-1 and matrix metalloproteinases in local tissues of the body, causing inflammatory cell infiltration and tissue damage. IL-17A can also promote the proliferation and differentiation of a variety of cells. Participate in the proliferation, maturation and chemotaxis of neutrophils. IL-17A has a synergistic effect on the activation of T cells and promotes the maturation of dendritic cells. Studies have shown that SFB in the intestine has a hook-like structure. The hook tip adheres to mouse intestinal epithelial cells to form endocytic vesicles, which quickly transport the bacterial protein of SFB from the top of the intestinal epithelial cells to the base, thereby promote production of serum amyloid A protein, which in turn makes DCs in the lamina propria of the mucosa produce IL-6 and IL-23 and induces the proliferation and differentiation of Th17 cells [85]. Some studies have shown that enterotoxigenic ETBF colonization of the colonic mucosa in mice causes an increase in the number of Th17 cells in the TME. Th17 cells produce cytokines that phosphorylate STAT3 in colorectal epithelial cells and tumour cells to promote colon tumorigenesis [86]. Besides, the decrease in the proportion of *Bifidobacteria* in the intestine inhibits the production of Th17 cells [87]. Another study reported that the dysbiosis of gut microbiota reduces the number of Th1 cells as well as the levels of Th1 cytokines, including IFN-γ, TNF-α, IL12p40 and IL12p35, and co-stimulators, such as CD80, CD86 and MHCII. All of the above-mentioned factors play an active role in tumour antigen presentation and tumour cell killing effects. Subsequently, subcutaneous melanomas develop in mouse models [88]. Therefore, microorganisms play different roles in the TME by increasing or decreasing Th cell populations (Figure 2d). Exploring the mechanism by which the microbiota changes Th cells in the TME is a promising approach to provide new strategies for tumour therapy.

CD8+ T cells

Although the molecular details are far from being fully understood, it is clear that having a healthy gut microbiome can ensure that T cells are widely activated against antigens and are activated as cytotoxic CD8+ T cells, infiltrating and attacking tumour cells [89]. A study found 11 strains of intestinal microbiota that can increase the level of CD8+ T cells, enhance the antitumour immune response mediated by it and inhibit tumour progression. The effect is the same as that of immune checkpoint inhibitors, even better [71]. Besides, butyrate directly improves the antitumour cytotoxic CD8+ T-cell response in an ID2-dependent manner in vitro and in vivo through IL-12 signalling pathway. Patients with tumours that respond to

oxaliplatin have higher serum butyrate levels than those who do not respond. This can also increase the expression and function of ID2 among CD8+ T cell. The study shows that the intestinal microbial metabolite butyrate promotes the effect of antitumour treatment through the ID2-dependent regulation of CD8+ T-cell immunity, suggesting that the intestinal microbial metabolite can be used as a part of cancer treatment [90]. *Bifidobacterium* has a positive regulatory effect on the anti-PD-L1 antibody of the checkpoint inhibitor. The therapeutic effect of *Bifidobacteria* alone is almost the same as that of anti-PD-L1 antibody. The combined use almost completely inhibits tumour growth. *Bifidobacteria* activate CD8+T cells and also have the ability to activate dendritic cells [91].

In summary, CD8+T cells can be activated by intestinal microbiota and their metabolites. CD8+T cells have been paid more and more attention as tumour killer cells. The combined application of CD8+T cells and immunotherapy is very promising in tumour treatment.

Dendritic cells (DC)

DCs are the antigen-presenting cells (APC) with the strongest antigen-presenting function known so far. Its biggest feature is that it can stimulate the activation and proliferation of naive T cells. Therefore, it is the initiator of specific immunity. They are divided into conventional dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs). The foremost function of cDCs is to secrete TNF and regulate the activation of T cells [92,93]. pDCs mainly secrete amount of type I interferons (IFN-Is) during virus infection [94].

Studies have shown that the intestinal microbiota can maintain basal state of DC by regulating type I interferon signals. The cDCs of GF mice do not produce sufficient TNF. The implantation of microbiota in the intestine of GF mice, even single bacteria, is sufficient to mediate the response of cDC to external stimuli and induce the secretion of TNF. Furthermore, compared with SPF mice, the IFN-I signalling pathway-related genes in GF mice (including Oas2, Socs2, Itga6, Itgav, Ifi35, Ifi205, Ifitm1 and Il15) and related Stat1 and IFNAR expression levels are relatively low through whole-genome RNA sequencing experiments. IFN-I that maintains basal state of DCs comes from pDCs, not cDCs. In addition, removing pDCs that secrete IFN-I significantly reduce the ability of cDCs to present antigens to CD8+ T cells. These results indicate that microbiota regulates the ability of pDCs to secrete IFN-I, thereby maintaining basal state of DCs. Further investigation found that the microbiota regulates the basal state of cDC through IFNAR signal [95]. *Bacteroides thetaiotaomicron* is an important member of the intestinal microbiota. As gram-negative bacteria, the outer membrane vesicles (Bt OMV) secreted by it can cross the intestinal epithelial barrier to mediate host–flora interaction, playing a role in maintaining intestinal homeostasis. Bt OMV induces the regulatory phenotype (such as IL-10 expression) of DCs isolated from healthy human colon and blood. However, the ability of the bacteria to induce the regulatory phenotype of the DCs of IBD patients is significantly reduced [96]. In addition, hepcidin secreted by cDC2s promotes healing of the intestinal mucosa after enteritis caused by microbiota [97]. In terms of antitumour, the intestinal microbiota regulates dendritic cell antigen presentation and the antitumour immune response induced by radiotherapy suggests a new mechanism. Elimination of short-chain fatty acid-producing bacteria helps to improve the antitumour efficacy mediated by vancomycin and radiotherapy. This is accompanied by the remodelling of the tumour microenvironment and the increase of antigen presentation and cytotoxic T-cell infiltration in the tumour [98]. Dendritic cells also play a key role in the clinical antitumour treatment of PD-L1 inhibitors [99].

In short, there are relatively few studies on DCs in the intestinal microbiota-tumour interaction. As the promoter of T cells, DCs have important immune function in the TME (Figure 2g). In future research, DCs are still a hot research topic in terms of repairing the intestinal mucosa and participating in immunity, especially in the interaction with the microbiota in the TME.

Natural killer cells (NK cells)

Most NK cells are cytotoxic. They produce lysed particles containing many molecules (including perforin, granzyme and granulysin in humans) that can induce the death of target cells. NK cells also express a variety of TNF superfamily members, such as FASL, TRAIL, and these molecules induce target cell apoptosis by binding to their corresponding receptors (FAS or TRAILR).

Studies have shown that *Lactobacillus plantarum* (*Lp*) stimulation of NK cells enhances IL-22 production, which in turn provides defence against enterotoxigenic *Escherichia coli* (ETEC)-induced damage to the intestinal epithelial barrier [100]. Besides, another study investigated and compared potential antitumour immune responses induced by *Lp*. *Lp* produced protective immunity by increasing CD8+ T cells and NK cell infiltration into TME, up-regulation of IFN-γ production, and promotion of Th1-type CD4+ T differentiation. Consequently, *Lp* enhances the antitumour immune response and delays tumour formation (Figure 2h).

There are relatively few studies on NK cells and microbiota in TME. More in-depth researches are needed.

Bystander effects in the microbiome-TME interactions

There is a very interesting phenomenon of radiobiology in the process of radiotherapy; that is, radiotherapy can not only kill the tumour cells that have been irradiated, but also the tumour cells that have not been irradiated around it. This phenomenon is called 'bystander effect' (BSE). BSE is characterized by genomic damage in target cells [101]. It also occurs when macrophages are chronically infected [102]. *Enterococcus faecalis* (*E. faecalis*) polarizes colon macrophages to an M1 phenotype. In addition, depleting M1 phenotype-macrophages with encapsulated liposomal clodronate (ELC) caused decrease of tumour necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2), netrin-1 and trans-4-hydroxy-2-nonenal (4-HNE). They are markers for BSE. TNF-α induces netrin-1, regulating intestinal epithelial cell apoptosis. COX-2 generates 4-HNE, an endogenous mutagen. BSE mediates DNA damage and induces chromosomal instability in neighbouring cells, promoting development of tumour. This suggests that M1 phenotype is the key effector for bacterial-induced BSE [103]. Further study suggests exposure of primary colon epithelial cells to commensal-polarized M1 phenotype-macrophages or 4-HNE induces heritable mutagenesis and initiate chromosomal instability (CIN). Gradually, colon epithelial cells express stem/progenitor cell markers Ly6A, Ly6E and tumour stem cell marker-doublecortin-like kinase 1 (Dclk1) in *E. faecalis*-colonized IL-10$^{-/-}$ mice [104]. *E. faecalis*-polarized macrophages induce gene mutation, CIN and endogenous transformation through BSE. Besides, another study shows BSE activates Wnt/β-catenin signalling and pluripotent transcription factors in colon epithelial cells, such as c-Myc, Klf4, Oct4 and Sox2. These factors are associated with dedifferentiation, reprogramming and the development of colorectal cancer stem cells (CSCs). Exposure of murine primary colon epithelial cells to *E. faecalis* -infected macrophages increased Wnt3α expression while suppressing Wnt inhibitor factor 1 (Wif1). This is mediated by 4-HNE and TNF-α, two mediators of BSE. Wnt/β-catenin activation was confirmed by increased active β-catenin and Tcf4. Nuclear β-catenin binds TCF4 and induces pluripotent transcription factors and CSC markers [105].

These findings provide mechanism for microbiome-induced colorectal cancer and identify new potential targets for colorectal cancer prevention (Figure 3).

THE RELATIONSHIP BETWEEN DIFFERENT TYPES OF BACTERIA AND TUMOURS

There are studies showing that tumours develop because of the disruption of gut microbiota caused by antibiotics, which is not always the case. Sethi et al. showed that gut microbiome depletion using antibiotics leads to a significant decrease in tumour burden in pancreatic cancer and melanoma. Gut microbiome depletion reduced liver metastasis from pancreatic cancer and colon cancer, as well

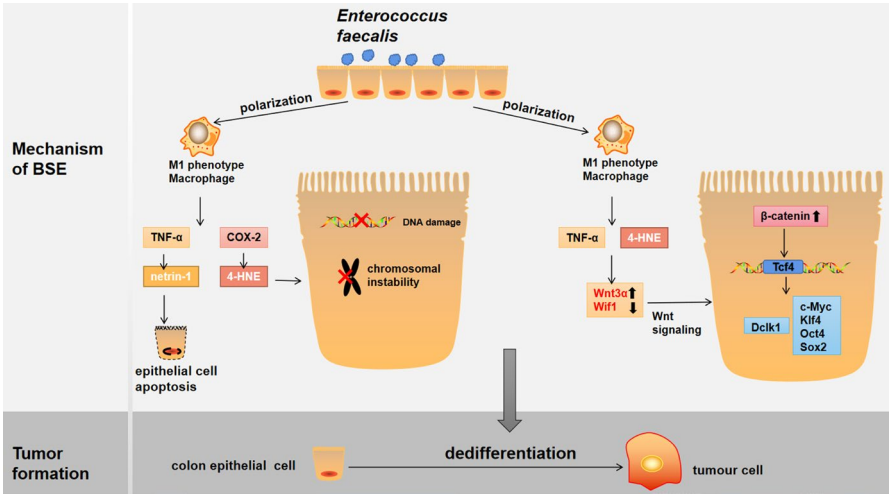

FIGURE 3 Mechanism of bystander effects (BSE) in the microbiome-TME interactions. *Enterococcus faecalis* polarizes colon macrophages to an M1 phenotype. M1 phenotype-macrophages induce increase of TNF-α, COX-2, netrin-1 and 4-HNE. TNF-α induces netrin-1, regulating intestinal epithelial cell apoptosis. COX-2 generates 4-HNE, mediating DNA damage, and induces chromosomal instability in neighbouring cells. 4-HNE and TNF-α increased Wnt3α expression while suppressing Wif1. They activate Wnt/β-catenin signalling. Nuclear β-catenin binds TCF4 and induces pluripotent transcription factors such as c-Myc, Klf4, Oct4, and Sox2, and Dclk1, which is CRC marker. These factors are associated with dedifferentiation, reprogramming and the development of colorectal cancer stem cells

TABLE 1 Diverse roles of intestinal microbiota across different cancers

Cancer types	Key microbiota	Roles in cancer	Underlying mechanism	
CRC	*Fusobacterium nucleatum*	Tumour promotion	Decreased CD3+ T cells and exerted antitumour effect	[72]
	Fusobacterium nucleatum	Tumour promotion	(1) Increased some immune cells of MDSC, TANs, TAMs and CD103+ regulatory DCs in TME to suppress antitumour immunity. (2) Activated NF-κB signalling pathway.	[66]
	Intestinal dysbacteriosis	Tumour promotion	Increased the secretion of IL-6 and TNF-α, which made contributions to EMT.	[53]
	Intestinal microbial LPS	Tumour promotion	Stimulated CD11b+ cells to increase c-Jun phosphorylation, accelerating CRC cell proliferation.	[54]
	Intestinal dysbacteriosis	Tumour promotion	CTSK enabled CRC cells to migrate and invasion via M2 macrophage-associated TLR4-mTOR- NF-κB signalling pathway in TME.	[56]
	Clostridium butyricum and Bacillus subtilis	Tumour suppression	Suppressed the proliferation of CRC cells, led to cell cycle arrest and promoted apoptosis	[107]
	Helicobacter hepaticus	Tumour suppression	Induce *H. hepaticus* -specific CD4+ T follicular T helper cells (TFH) and the TFH-dependent formation of tertiary lymphoid structures (TLS) within and around tumours.	[108]
	Escherichia coli NC101 (*E. coli* NC101)	Tumour promotion	*E. coli* NC101-derived pks promotes DNA damage, accelerating progression from dysplasia to invasive carcinoma in AOM/Il10$^{-/-}$ mice.	[109]
Pancreatic carcinoma	*Saccharopolyspora, Pseudoxanthomonas and Streptomyces*	Predict prognosis	Contributed to the antitumour immune response by favouring recruitment and activation of CD8+ T cells.	[12]
Melanoma	11 types of certain intestinal microorganisms	Tumour suppression	Activated the immune system of tumour model mice and enhanced their antitumour immune response.	[110]
Hepatocellular carcinoma	Intestinal dysbacteriosis	Tumour promotion	Induced hyperplasia of colonic epithelial tuft cells and promoted the production of IL-25 derived from tuft cells. IL-25 facilitated HCC cell migration and invasion, and activate M2 macrophages in TME.	[55]
	Helicobacter hepaticus	Tumour promotion	Facilitated tumour cell proliferation. Activated Wnt/β-catenin and NF-κB signalling pathway to account for liver tumour progression.	[111]
	Escherichia coli	Promote colorectal cancer metastasis to liver	*Escherichia coli* drives mouse gut vascular barrier injury through VirF, a virulence regulator, and reaches the liver to promote premetastatic niche (PMN) formation. PMN enhances the recruitment of metastatic cancer cells.	[112]
Prostate cancer	*Helicobacter hepaticus*	Tumour promotion	Induced the production of TNF-α and IL-1α, thereby activating the NF-κB signalling pathway and promoting the occurrence of prostate cancer.	[113–116]

(Continues)

TABLE 1 (Continued)

Cancer types	Key microbiota	Roles in cancer	Underlying mechanism	
Breast cancer	*Lactobacillus reuteri*	Tumour suppression	Prevented nuclear translocation of NF-κB-p65 and c-jun and reduced the resistance of HER2/neu tumour cells to apoptosis,	[80]
	Helicobacter hepaticus	Dual role at different times	$Rag2^{-/-}$C57BL/6 $Apc^{Min/+}$ mice infected with intestinal bacterial pathogen Helicobacter hepaticus had more rapid breast cancer. Mice that previously exposed to Helicobacter hepaticus could significantly improve the antitumour ability of Treg cells in TME.	[52]
	Intestinal dysbacteriosis	Tumour promotion	Increased the infiltration of macrophages into the breast TME and made hormone receptor-positive breast cancer more aggressive by regulating the immune system. Led to reduction the stimulation of bacterial-dependent immune cells and formed a permissive environment for breast tumours.	[28,29]
Multiple myeloma	*Prevotella heparinolytica*	Tumour promotion	Activated Th17 cells to produce IL-17, inducing the phosphorylation of STAT3 in mouse plasma cells and the activation of eosinophils in TME.	[117]

as melanoma in mouse models. Interestingly, the effect of shrinking tumours is not through direct toxic effects on tumours but through the involvement of adaptive immunity [106]. In addition to the overall imbalance of intestinal microbiota in the TME, specific microbiota in the intestinal microecology have an impact on different types of tumour through immunity. The diverse roles of microbiota across different tumours are summarized in Table 1.

CLINICAL APPLICATIONS

The progress of clinical cancer treatment and clinical trials basing on the crosstalks between gut microbiota and immunity and significance

For most patients with advanced disease, cytotoxic drugs are the main treatment. However, these drugs cause high morbidity, mortality and unavoidable drug resistance associated with treatment [118], which are disadvantages of drug therapy. The intestinal microbiota provides a novel way to enhance the efficacy of current cancer drugs, reduce toxicity and increase sensitivity to immunotherapy [91]. The intestinal microbiota affects the efficiency of cancer drugs through several key mechanisms: metabolism, immune regulation, translocation, enzymatic degradation and ecological variation. A study suggests disruption of the microbiota impairs the response of subcutaneous tumours to CpG-oligonucleotide immunotherapy and platinum chemotherapy. Optimal responses to cancer therapy require an intact commensal microbiota that mediates its effects by modulating myeloid-derived cell functions in TME [89]. The emergence of immune checkpoint inhibitors to launch effective tumour attacks by lifting the brake mechanism of the body's immune system is a major breakthrough in the field of cancer treatment [119,120]. Studies have confirmed that the intestinal microbiota effectively improve the success of antitumour CD8+ T-cell reinfusion [71]. The use of antibiotics to reduce the host's intestinal microbiota will significantly reduce tumour suppression. Infusion of microbial ligand plasma to test mice can enhance CD8+ T-cell activation and promote tumour shrinkage. Probiotics are a type of host beneficial active microorganisms colonized in the human intestines, reproductive system, oral cavity, oesophagus, etc. They reduce the pH of the intestines by producing organic acids, inhibit the growth of pathogenic bacteria and maintain the intestines, etc. The inherent microbiota of the tract maintains the balance of the microbiota in the intestinal tract, thereby further regulating the body's immune function [121].

Therefore, the regulation and intervention of intestinal microbiota are of great significance in the treatment of

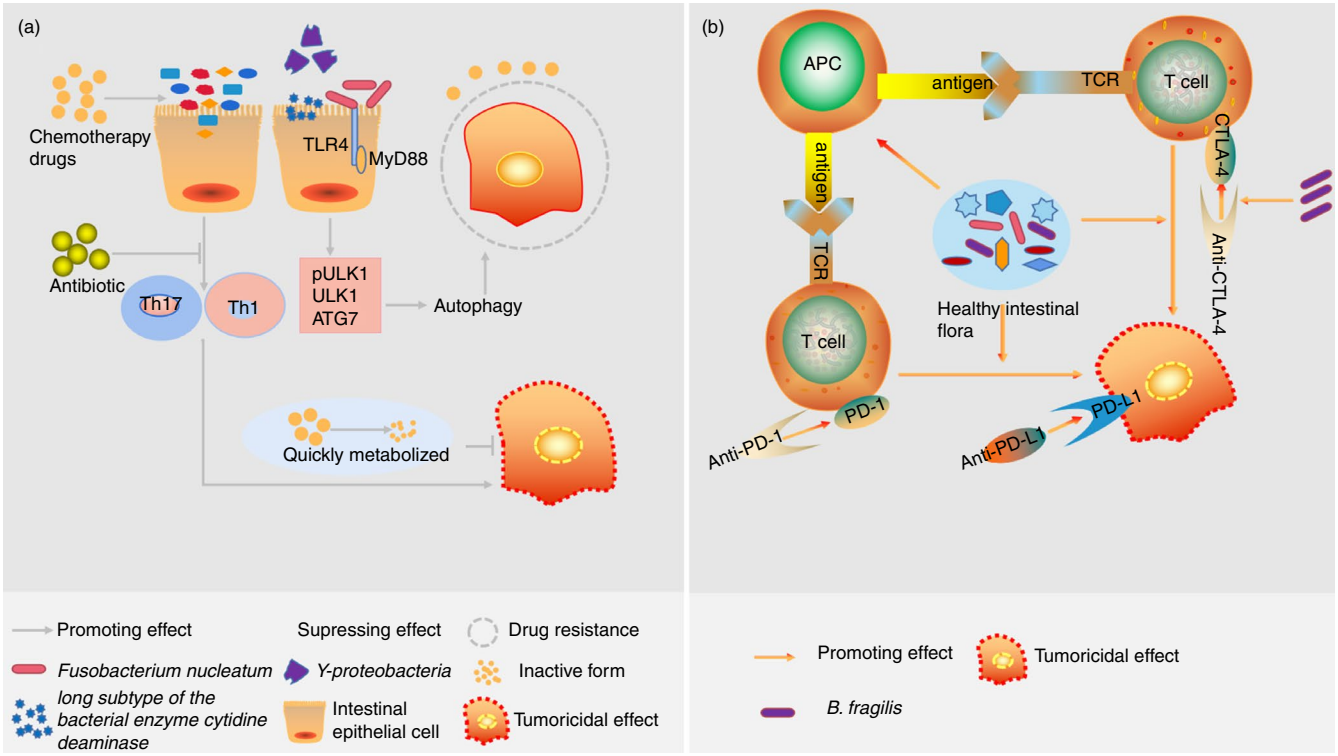

FIGURE 4 Effects of intestinal microbiota on tumour drug resistance and immunotherapy. (a) Effect of the intestinal microbiota on tumour drug resistance. Chemotherapy drugs destroy the intestinal mucosa, cause intestinal microbiota translocation, induce antitumoral Th1 and Th17 immune responses and ultimately enhance tumoricidal effects. γ-Proteobacteria can express the long subtype of the bacterial enzyme cytidine deaminase, metabolizing a chemotherapy drug to its inactive form. *F. nucleatum* stimulates the expression of autophagy-related proteins such as pULK1, ULK1 and ATG7 through the TLR4 and MYD88 signalling pathways, resulting in CRC chemoresistance. (b) Effects of intestinal microbiota on immunotherapy. A healthy intestinal microbiota can activate APCs. APCs activate T cells through antigen presentation. Activated T cells express PD-1 and CTLA-4. A healthy intestinal microbiota promotes the binding of anti-PD-1 to PD-1 and anti-CTLA-4 to CTLA-4, inhibits the inactivation of T cells and exerts tumour-killing effects. A healthy intestinal microbiota can promote the binding of anti-PD-L1 to PD-L1 expressed by tumour cells, thereby inhibiting the binding of PD-L1 to T cells and indirectly exerting antitumour effects. B. fragilis enhanced the effect of the CTLA-4 Ab

various types of cancer. In the future, therapeutic intervention for the microbiota will be one of the next areas for precise and personalized treatment of cancer.

Intestinal microbiota affect drug resistance in tumours

Increasing evidence shows that intestinal microbiota affect the treatment effect of anticancer drugs (Figure 4a). For example, some bacteria cause drug resistance in patients. *F. nucleatum* has been reported to promote CRC [122]. However, its effect on the tumour extends beyond this finding. *F. nucleatum* stimulates the expression of the autophagy-related proteins pULK1, ULK1 and ATG7 in CRC via the loss of miR-18a* and miR-4802 dependent on the TLR4 and MYD88 signalling pathways, subsequently resulting in CRC chemoresistance. These results remind us that the combination of chemotherapy and anti-*F. nucleatum* treatment or an autophagy inhibitor for CRC patients may be an ideal treatment choice [123]. In addition, gemcitabine is a commonly used drug for the treatment of pancreatic ductal adenocarcinoma (PDAC), and γ-proteobacteria in pancreatic tumours are also involved in the resistance to gemcitabine [124]. Cyclophosphamide has been verified to destroy the intestinal mucosa, cause intestinal microbiota translocation, induce antitumour Th1 and Th17 immune responses and ultimately benefit tumour treatment. Antibiotics cause a reduction in the abundance of intestinal microbiota in mice. This change affects the conversion of CD4+ T cells to antitumoral Th1 and Th17 cells, leading to the failure of anticancer drugs [125]. Therefore, with the widespread emergence of tumour resistance to chemotherapy drugs, maintaining or restoring the intestinal microecology, restoring immunity and producing synergistic effects with chemotherapy drugs may have great potential for remodelling the TME and improving the efficacy of chemotherapy drugs.

Effects of intestinal microbiota on immunotherapy

Intestinal microbiota are closely associated with intestinal immunity and affect the systemic immune system. Healthy intestinal microbiota activate T cells through antigen presentation by APCs [126]. T cells activated by APCs express PD-1 and CTLA-4 [127]. This expression prevents immune damage caused by the excessive activation of T cells [25,128]. However, tumour cells usually express PD-L1, which has inappropriate inhibitory effects on T cells, promoting tumorigenesis [24,129]. CTLA-4 molecules are highly expressed on activated T lymphocytes; they share the B7 molecular ligand of antigen-presenting cells (APCs) with CD28. T cells are induced to be non-responsive and participate in the negative regulation of the immune response. CTLA-4 is overexpressed in a variety of cancers, leading to uncontrolled tumour growth [130]. Recent studies have shown that gut microbiota affect the efficacy of tumour immunotherapy, especially PD-1 and CTLA-4 blockade (Figure 4b). One study showed that gut microbiota mediate anticancer immunotherapy by collaborating with the CTLA-4 blockade. In mice orally fed *B. fragilis*, Th1 immune responses in the tumour-draining lymph nodes were increased. *B. fragilis* also promoted the maturation of tumoral DCs, which culminated in the restoration of the therapeutic response of GF tumour bearers to a CTLA-4 Ab [131].

Intestinal microbiota have great potential for the PD-1/PD-L1-mediated treatment of tumours

PD-1 is an important co-inhibitory molecule expressed in activated T cells, and its ligands are PD-L1 and PD-L2. When PD-1 combines with a ligand, it inhibits the proliferation of T cells and the production of cytokines, such as IL-2 and IFN-γ, as well as the proliferation and differentiation of B cells and the secretion of Ig. Recently, immunotherapy targeting the PD-1/PD-L1 axis has delivered favourable results in many tumours, especially solid tumours [119,120,132]. Studies have demonstrated that the antitumour effects are achieved through the interaction between IFN-γ^+ CD8+T cells and immune checkpoint inhibitors (ICIs) [130,133]. One study in a mouse model suggested that the efficacy of anti-PD-1 treatment via the production of IFN-γ^+ CD8 T cells was greater in GF+11-mix mice orally administered 11 strains of microbiota than in GF+10-mix or germ-free mice [71]. Researchers transplanted faecal microbial microbiota (FMT) from cancer patients who responded to ICI into sterile or antibiotic-treated tumour-bearing mice and found that the antitumour effect of PD-1 blockers was enhanced. The faecal microbiota of patients who did not respond to ICI did not have this effect. Enriched *A. muciniphila* was detected in the stool of patients who responded to ICI [134]. In addition, *Bifidobacterium* is also associated with antitumour effects in mice. The oral administration of *Bifidobacteria* alone has been shown to induce the same effect as anti-PD-L1 treatment. The combination of the two treatments almost completely inhibited tumour growth. *Bifidobacterium* has been shown to enhance the activation of CD8+ T cells and the functions of DC cells gathered in the tumour microenvironment, consequently producing a combined antitumour effect with PD-L1 [91]. Another study used 16S rRNA sequencing, metagenomic shotgun sequencing and Q-PCR to determine the gene sequences of microorganisms in patients with melanoma treated with PD-1 antibodies. The increased abundance of bacteria, including *Bifidobacterium longum*, *Enterococcus aerogenes* and *Enterococcus faecalis*, was found in the faeces of patients who were responsive to PD-1 antibody treatment. Transferring the faeces of responders to sterile mice improved tumour control, enhanced the T-cell response and improve the efficacy of anti-PD-L1 treatment [135]. 16S ribosome RNA gene sequencing was used to evaluate the intestinal microbe distribution of patients with advanced non-small-cell lung cancer treated with a PD-1 monoclonal antibody. Responsive patients had increased diversity of intestinal microbiota and enriched *Alistipes putredinis*, *Bifidobacterium longum* and *Prevotella copri* during the treatment process. Subsequently, patients with high microbiome diversity had significantly longer progression-free survival than patients with low diversity [136]. A similar phenomenon was also found in metastatic melanoma. Eight species of *Enterococcus faecium*, *Collinsella aerofaciens*, *Bifidobacterium adolescentis*, *Klebsiella pneumoniae*, *Veillonella parvula*, *Parabacteroides merdae*, *Lactobacillus sp.* and *Bifidobacterium longum* were enriched in patients who responded to PD-1 antibody treatment. *Ruminococcus obeum* and *Roseburia intestinalis* were enriched in non-responsive patients. Transplanting sterile mice with faecal bacteria from patients who respond to PD-1 antibody significantly improve tumour control, enhance T-cell responses and obtain better efficacy. In summary, there is a significant correlation between the composition of the patient's microbiota and the effect of anti-PD-1 immunotherapy. Specific microbiota affect the antitumour immunity of cancer patients and can be used as a biomarker to predict whether patients are responsive to immune checkpoint blocking therapy [137].

Specific intestinal microbiota participate in or affect the tumour immune process, which has an effect on the efficacy of PD-1 antibodies (Figure 4b). From the clinical practice perspective, perhaps one day, supplementation with specific intestinal bacterial groups that are beneficial for the function of PD-1 antibodies or specific faecal transplants may increase the effectiveness

of immunotherapy. In addition, the effect of immunotherapy can also be predicted by the examination of intestinal bacteria. Regardless, gut microbiota have great potential for providing more information for clinical practice.

Clinical application of antibiotics and probiotics

Escherichia coli metabolize the chemotherapy drug gemcitabine to its inactive form. This drug metabolism depends on the expression of the long subtype of the bacterial enzyme cytidine deaminase (CDDL), which is mainly found in γ-proteobacteria. In a mouse model of colon cancer, gemcitabine resistance was induced by intratumoral γ-proteobacteria, which depended on the expression of bacterial CDDL. Antibiotics eliminated this resistance. In addition, antibiotics affect the conversion of CD4+ T cells to antitumoral Th1 and Th17 cells, leading to the failure of anticancer drugs (Figure 4a).

Another study showed that EcN, a widely used probiotic, can work in concert with the transforming growth factor (TGF-β) blocker galunisertib (Gal) to exert antitumour effects. When both are used, they increase IL-2 and IFN-γ expression in the TME and reduce TGF-β and IL-10 expression. The synergy between EcN and galunisertib increases apoptosis and inhibits the tumour metastasis and angiogenesis mediated by changes in the intestinal microbiota [138]. In brief, most intestinal probiotics exert antitumour effects by promoting immunotherapy in the TME.

CONCLUSION

The intestinal microecology, immunity and TME are closely related. The intestinal microecology, especially intestinal microbiota, can affect immunity to remodel the TME through various mechanisms, such as STAT3, NF-κB, JNK and TLR4-mTOR. A variety of cytokines also affect intestinal and extra-intestinal tumours as mediators. Harmful microbiota and intestinal microecological imbalances often promote tumour development and the development of tumour resistance. The use of probiotics can restore the intestinal microecology and have a synergistic effect with PD-1/PD-L1 inhibitors on tumour treatment. However, there are still many problems in this field that need to be explored. First, individual differences exist. In addition, the composition and regulation of the TME are very complicated. Furthermore, the large number of intestinal microbiota, which directly or indirectly affect intestinal microecological changes in cancer patients, are difficult to study. An in-depth analysis of the interactions of the intestinal microecology, immunity and the tumour microenvironment, will facilitate the screening of tumour sensitivity to drugs and improve tumour therapeutic effects in the future.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

ZQS, YXG, CC, QBZ, LYZ, BS, GXW, JBL and WTY conceived the structure of manuscript and revised the manuscript. XXY drafted initial manuscript. XXY made the figures and table. All authors read and approved the final manuscript.

ORCID

Weitang Yuan https://orcid.org/0000-0003-2866-6261

REFERENCES

1. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012;489:220–30.
2. Zhou C, Zhao H, Xiao XY, Chen BD, Guo RJ, Wang Q, et al. Metagenomic profiling of the pro-inflammatory gut microbiota in ankylosing spondylitis. J Autoimmun. 2020;107:102360.
3. Primec M, Klemenak M, Di Gioia D, Aloisio I, Bozzi Cionci N, Quagliariello A, et al. Clinical intervention using Bifidobacterium strains in celiac disease children reveals novel microbial modulators of TNF-α and short-chain fatty acids. Clin Nutr. 2019;38:1373–81.
4. Arnoriaga-Rodríguez M, Mayneris-Perxachs J, Burokas A, Contreras-Rodríguez O, Blasco G, Coll C, et al. Obesity impairs short-term and working memory through gut microbial metabolism of aromatic amino acids. Cell Metab. 2020;32:548–60.e7.
5. Bashir M, Prietl B, Tauschmann M, Mautner SI, Kump PK, Treiber G, et al. Effects of high doses of vitamin D3 on mucosa-associated gut microbiome vary between regions of the human gastrointestinal tract. Eur J Nutr. 2016;55:1479–89.
6. Cervantes-Barragan L, Chai JN, Tianero MD, Di Luccia B, Ahern PP, Merriman J, et al. Lactobacillus reuteri induces gut intraepithelial CD4(+)CD8alphaalpha(+) T cells. Science. 2017;357:806–10.
7. Scott NA, Andrusaite A, Andersen P, Lawson M, Alcon-Giner C, Leclaire C, et al. Antibiotics induce sustained dysregulation of intestinal T cell immunity by perturbing macrophage homeostasis. Sci Transl Med. 2018;10:eaao4755.
8. Chen D, Jin D, Huang S, Wu J, Xu M, Liu T, et al. Clostridium butyricum, a butyrate-producing probiotic, inhibits intestinal tumor development through modulating Wnt signaling and gut microbiota. Cancer Lett. 2020;469:456–67.
9. Maini Rekdal V, Bess EN, Bisanz JE, Turnbaugh PJ, Balskus EP. Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism. Science. 2019;364(6445):eaau6323.
10. Balakumar M, Prabhu D, Sathishkumar C, Prabu P, Rokana N, Kumar R, et al. Improvement in glucose tolerance and insulin sensitivity by probiotic strains of Indian gut origin in high-fat diet-fed C57BL/6J mice. Eur J Nutr. 2018;57:279–95.

11. Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature. 2019;570:462–7.
12. Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, et al. Tumor microbiome diversity and composition influence pancreatic cancer outcomes. Cell. 2019;178:795–806.e12.
13. Nejman D, Livyatan I, Fuks G, Gavert N, Zwang Y, Geller LT, et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science. 2020;368:973–80.
14. Kuo C-L, Chou H-Y, Chiu Y-C, Cheng AN, Fan C-C, Chang Y-N, et al. Mitochondrial oxidative stress by Lon-PYCR1 maintains an immunosuppressive tumor microenvironment that promotes cancer progression and metastasis. Cancer Lett. 2020;474:138–50.
15. Chen X, Zhang L, Zhang IY, Liang J, Wang H, Ouyang M, et al. RAGE expression in tumor-associated macrophages promotes angiogenesis in glioma. Can Res. 2014;74:7285–97.
16. Sakamoto S, Kagawa S, Kuwada K, Ito A, Kajioka H, Kakiuchi Y, et al. Intraperitoneal cancer-immune microenvironment promotes peritoneal dissemination of gastric cancer. Oncoimmunology. 2019;8(12):e1671760.
17. Weng Y-S, Tseng H-Y, Chen Y-A, Shen P-C, Al Haq AT, Chen L-M, et al. MCT-1/miR-34a/IL-6/IL-6R signaling axis promotes EMT progression, cancer stemness and M2 macrophage polarization in triple-negative breast cancer. Mol Cancer. 2019;18(1):42.
18. Li W, Wang H, Ma Z, Zhang J, Ou-Yang W, Qi Y, et al. Multi-omics analysis of microenvironment characteristics and immune escape mechanisms of hepatocellular carcinoma. Front Oncol. 2019;9:1019.
19. Wang J, Sun J, Liu LN, Flies DB, Nie X, Toki M, et al. Siglec-15 as an immune suppressor and potential target for normalization cancer immunotherapy. Nat Med. 2019;25:656–66.
20. Wong T-L, Ng K-Y, Tan KV, Chan L-H, Zhou L, Che N, et al. CRAF methylation by PRMT6 regulates aerobic glycolysis-driven hepatocarcinogenesis via ERK-dependent PKM2 nuclear relocalization and activation. Hepatology. 2020;71(4):1279–96. https://doi.org/10.1002/hep.30923
21. Loo JM, Scherl A, Nguyen A, Man FY, Weinberg E, Zeng Z, et al. Extracellular metabolic energetics can promote cancer progression. Cell. 2015;160:393–406.
22. Ngwa VM, Edwards DN, Philip M, Chen J. Microenvironmental metabolism regulates antitumor immunity. Can Res. 2019;79:4003–8.
23. Turajlic S, Litchfield K, Xu H, Rosenthal R, McGranahan N, Reading JL, et al. Insertion-and-deletion-derived tumour-specific neoantigens and the immunogenic phenotype: a pan-cancer analysis. Lancet Oncol. 2017;18:1009–21.
24. Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, McCracken MN, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nature. 2017;545:495–9.
25. Rosskopf S, Jahn-Schmid B, Schmetterer KG, Zlabinger GJ, Steinberger P. PD-1 has a unique capacity to inhibit allergen-specific human CD4(+) T cell responses. Sci Rep. 2018;8:13543.
26. Arce Vargas F, Furness AJS, Litchfield K, Joshi K, Rosenthal R, Ghorani E, et al. Fc effector function contributes to the activity of human anti-CTLA-4 antibodies. Cancer Cell. 2018;33:649–63.e4.
27. Ma C, Han M, Heinrich B, Fu Q, Zhang Q, Sandhu M, et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science. 2018;360(6391):eaan5931.
28. Xuan C, Shamonki JM, Chung A, Dinome ML, Chung M, Sieling PA, et al. Microbial dysbiosis is associated with human breast cancer. PLoS One. 2014;9:e83744.
29. Buchta Rosean C, Bostic RR, Ferey JCM, Feng TY, Azar FN, Tung KS, et al. Preexisting commensal dysbiosis is a host-intrinsic regulator of tissue inflammation and tumor cell dissemination in hormone receptor-positive breast cancer. Cancer Res. 2019;79:3662–75.
30. Vukman KV, Adams PN, Metz M, Maurer M, O'Neill SM. Fasciola hepatica tegumental coat impairs mast cells' ability to drive Th1 immune responses. J Immunol. 2013;190:2873–9.
31. Kumar V, Donthireddy L, Marvel D, Condamine T, Wang F, Lavilla-Alonso S, et al. Cancer-associated fibroblasts neutralize the anti-tumor effect of CSF1 receptor blockade by inducing PMN-MDSC infiltration of tumors. Cancer Cell. 2017;32:654–68.e5.
32. Zhang Y, Diao N, Lee CK, Chu HW, Bai L, Li L. Neutrophils deficient in innate suppressor IRAK-M Enhances Anti-tumor Immune Responses. Mol Ther. 2020;28(1):89–99.
33. Harada M, Matsunaga K, Oguchi Y, Iijima H, Ito O, Tamada K, et al. The involvement of transforming growth factor beta in the impaired antitumor T-cell response at the gut-associated lymphoid tissue (GALT). Cancer Res. 1995;55:6146–51.
34. Harada M, Matsunaga K, Oguchi Y, Iijima H, Tamada K, Abe K, et al. Oral administration of PSK can improve the impaired anti-tumor CD4+ T-cell response in gut-associated lymphoid tissue (GALT) of specific-pathogen-free mice. Int J Cancer. 1997;70:362–72.
35. Monteleone G, Holloway J, Salvati VM, Pender SL, Fairclough PD, Croft N, et al. Activated STAT4 and a functional role for IL-12 in human Peyer's patches. J Immunol. 2003;170:300–7.
36. Pruteanu M, Hyland NP, Clarke DJ, Kiely B, Shanahan F. Degradation of the extracellular matrix components by bacterial-derived metalloproteases: implications for inflammatory bowel diseases. Inflamm Bowel Dis. 2011;17:1189–200.
37. Kohl KD, Oakeson KF, Orr TJ, Miller AW, Forbey JS, Phillips CD, et al. Metagenomic sequencing provides insights into microbial detoxification in the guts of small mammalian herbivores (Neotoma spp.). FEMS Microbiol Ecol. 2018;94:fiy184.
38. Levy M, Thaiss CA, Zeevi D, Dohnalova L, Zilberman-Schapira G, Mahdi JA, et al. Microbiota-modulated metabolites shape the intestinal microenvironment by regulating NLRP6 inflammasome signaling. Cell. 2015;163:1428–43.
39. Nagatake T, Hirata SI, Koga T, Kuroda E, Kobari S, Suzuki H, et al. BLT1 mediates commensal bacteria-dependent innate immune signals to enhance antigen-specific intestinal IgA responses. Mucosal Immunol. 2019;12:1082–91.
40. Goto Y, Panea C, Nakato G, Cebula A, Lee C, Diez MG, et al. Segmented filamentous bacteria antigens presented by intestinal dendritic cells drive mucosal Th17 cell differentiation. Immunity. 2014;40:594–607.
41. Otte JM, Cario E, Podolsky DK. Mechanisms of cross hyporesponsiveness to Toll-like receptor bacterial ligands in intestinal epithelial cells. Gastroenterology. 2004;126:1054–70.
42. Moriez R, Salvador-Cartier C, Theodorou V, Fioramonti J, Eutamene H, Bueno L. Myosin light chain kinase is involved in lipopolysaccharide-induced disruption of colonic epithelial barrier and bacterial translocation in rats. Am J Pathol. 2005;167:1071–9.
43. Nigro G, Rossi R, Commere PH, Jay P, Sansonetti PJ. The cytosolic bacterial peptidoglycan sensor Nod2 affords stem cell

protection and links microbes to gut epithelial regeneration. Cell Host Microbe. 2014;15:792–8.
44. Jing X, Zulfiqar F, Park SY, Núñez G, Dziarski R, Gupta D. Peptidoglycan recognition protein 3 and Nod2 synergistically protect mice from dextran sodium sulfate-induced colitis. J Immunol. 2014;193:3055–69.
45. Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. Nat Med. 2010;16:228–31.
46. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013;341:569–73.
47. Vieira AT, Galvão I, Macia LM, Sernaglia ÉM, Vinolo MA, Garcia CC, et al. Dietary fiber and the short-chain fatty acid acetate promote resolution of neutrophilic inflammation in a model of gout in mice. J Leukoc Biol. 2017;101:275–84.
48. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell. 2005;122:107–18.
49. He B, Hoang TK, Wang T, Ferris M, Taylor CM, Tian X, et al. Resetting microbiota by Lactobacillus reuteri inhibits T reg deficiency-induced autoimmunity via adenosine A2A receptors. J Exp Med. 2017;214:107–23.
50. Mager LF, Burkhard R, Pett N, Cooke NCA, Brown K, Ramay H, et al. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. Science. 2020;369:1481–9.
51. Shi Y, Zheng W, Yang K, Harris KG, Ni K, Xue L, et al. Intratumoral accumulation of gut microbiota facilitates CD47-based immunotherapy via STING signaling. J Exp Med. 2020;217:2282.
52. Rao VP, Poutahidis T, Ge Z, Nambiar PR, Boussahmain C, Wang YY, et al. Innate immune inflammatory response against enteric bacteria Helicobacter hepaticus induces mammary adenocarcinoma in mice. Cancer Res. 2006;66:7395–400.
53. Wan G, Xie M, Yu H, Chen H. Intestinal dysbacteriosis activates tumor-associated macrophages to promote epithelial-mesenchymal transition of colorectal cancer. Innate Immun. 2018;24:480–9.
54. Li Y, Kundu P, Seow SW, de Matos CT, Aronsson L, Chin KC, et al. Gut microbiota accelerate tumor growth via c-jun and STAT3 phosphorylation in APCMin/+ mice. Carcinogenesis. 2012;33:1231–8.
55. Li Q, Ma L, Shen S, Guo Y, Cao Q, Cai X, et al. Intestinal dysbacteriosis-induced IL-25 promotes development of HCC via alternative activation of macrophages in tumor microenvironment. J Exp Clin Cancer Res. 2019;38:303.
56. Li R, Zhou R, Wang H, Li W, Pan M, Yao X, et al. Gut microbiota-stimulated cathepsin K secretion mediates TLR4-dependent M2 macrophage polarization and promotes tumor metastasis in colorectal cancer. Cell Death Differ. 2019;26:2447–63.
57. Huang J, Sun R, Qi X, Liu L, Yang Y, Sun B. Effect of autophagy on expression of neutrophil programmed death ligand-1 in mice with sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2019;31:1091–6.
58. Trump LR, Nayak RC, Singh AK, Emberesh S, Wellendorf AM, Lutzko CM, et al. Neutrophils derived from genetically modified human induced pluripotent stem cells circulate and phagocytose bacteria in vivo. Stem Cells Transl Med. 2019;8:557–67.
59. Havixbeck JJ, Rieger AM, Churchill LJ, Barreda DR. Neutrophils exert protection in early Aeromonas veronii infections through the clearance of both bacteria and dying macrophages. Fish Shellfish Immunol. 2017;63:18–30.
60. Triner D, Devenport SN, Ramakrishnan SK, Ma X, Frieler RA, Greenson JK, et al. Neutrophils restrict tumor-associated microbiota to reduce growth and invasion of colon tumors in mice. Gastroenterology. 2019;156:1467–82.
61. Miksch RC, Schoenberg MB, Weniger M, Bosch F, Ormanns S, Mayer B, et al. Prognostic impact of tumor-infiltrating lymphocytes and neutrophils on survival of patients with upfront resection of pancreatic cancer. Cancers (Basel). 2019;11:39.
62. Lakritz JR, Poutahidis T, Mirabal S, Varian BJ, Levkovich T, Ibrahim YM, et al. Gut bacteria require neutrophils to promote mammary tumorigenesis. Oncotarget. 2015;6:9387–96.
63. Erdman SE, Rao VP, Poutahidis T, Rogers AB, Taylor CL, Jackson EA, et al. Nitric oxide and TNF-alpha trigger colonic inflammation and carcinogenesis in Helicobacter hepaticus-infected, Rag2-deficient mice. Proc Natl Acad Sci USA. 2009;106:1027–32.
64. Abrams SI, Waight JD. Identification of a G-CSF-Granulocytic MDSC axis that promotes tumor progression. Oncoimmunology. 2012;1:550–1.
65. Thiele Orberg E, Fan H, Tam AJ, Dejea CM, Destefano Shields CE, Wu S, et al. The myeloid immune signature of enterotoxigenic Bacteroides fragilis-induced murine colon tumorigenesis. Mucosal Immunol. 2017;10:421–33.
66. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe. 2013;14:207–15.
67. Harusato A, Viennois E, Etienne-Mesmin L, Matsuyama S, Abo H, Osuka S, et al. Early-Life Microbiota Exposure Restricts Myeloid-Derived Suppressor Cell-Driven Colonic Tumorigenesis. Cancer Immunol Res. 2019;7:544–51.
68. Shin J, Monti S, Aires DJ, Duvic M, Golub T, Jones DA, et al. Lesional gene expression profiling in cutaneous T-cell lymphoma reveals natural clusters associated with disease outcome. Blood. 2007;110:3015–27.
69. Campbell JJ, Clark RA, Watanabe R, Kupper TS. Sezary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. Blood. 2010;116:767–71.
70. Dong M, Meng Z, Kuerban K, Qi F, Liu J, Wei Y, et al. Diosgenin promotes antitumor immunity and PD-1 antibody efficacy against melanoma by regulating intestinal microbiota. Cell Death Dis. 2018;9:1039.
71. Tanoue T, Morita S, Plichta DR, Skelly AN, Suda W, Sugiura Y, et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. Nature. 2019;565:600–5.
72. Mima K, Sukawa Y, Nishihara R, Qian ZR, Yamauchi M, Inamura K, et al. Fusobacterium nucleatum and T Cells in Colorectal Carcinoma. JAMA Oncol. 2015;1:653–61.
73. Chen M, Chen X, Wan Q. Altered frequency of Th17 and Treg cells in new-onset systemic lupus erythematosus patients. Eur J Clin Invest. 2018;48:e13012.
74. Zheng X, Zhang L, Chen J, Gu Y, Xu J, Ouyang Y. Dendritic cells and Th17/Treg ratio play critical roles in pathogenic process of chronic obstructive pulmonary disease. Biomed Pharmacother. 2018;108:1141–51.

75. Akesson K, Tompa A, Ryden A, Faresjo M. Low expression of CD39(+) /CD45RA(+) on regulatory T cells (Treg) cells in type 1 diabetic children in contrast to high expression of CD101(+) /CD129(+) on Treg cells in children with coeliac disease. Clin Exp Immunol. 2015;180:70–82.
76. Bergmann C, Wild CA, Narwan M, Lotfi R, Lang S, Brandau S. Human tumor-induced and naturally occurring Treg cells differentially affect NK cells activated by either IL-2 or target cells. Eur J Immunol. 2011;41:3564–73.
77. Yang Z, Zhang B, Li D, Lv M, Huang C, Shen GX, et al. Mast cells mobilize myeloid-derived suppressor cells and Treg cells in tumor microenvironment via IL-17 pathway in murine hepatocarcinoma model. PLoS One. 2010;5:e8922.
78. Downs-Canner S, Berkey S, Delgoffe GM, Edwards RP, Curiel T, Odunsi K, et al. Suppressive IL-17A(+)Foxp3(+) and ex-Th17 IL-17A(neg)Foxp3(+) Treg cells are a source of tumour-associated Treg cells. Nat Commun. 2017;8:14649.
79. Li Q, Yan J, Mao AP, Li C, Ran Y, Shu HB, et al. Tripartite motif 8 (TRIM8) modulates TNFalpha- and IL-1beta-triggered NF-kappaB activation by targeting TAK1 for K63-linked polyubiquitination. Proc Natl Acad Sci USA. 2011;108:19341–6.
80. Lakritz JR, Poutahidis T, Levkovich T, Varian BJ, Ibrahim YM, Chatzigiagkos A, et al. Beneficial bacteria stimulate host immune cells to counteract dietary and genetic predisposition to mammary cancer in mice. Int J Cancer. 2014;135:529–40.
81. Middleton D, Garza JJ, Greiner SP, Bowdridge SA. Neutrophils rapidly produce Th2 cytokines in response to larval but not adult helminth antigen. Parasite Immunol. 2019;42:e12679.
82. Tie R, Li H, Cai S, Liang Z, Shan W, Wang B, et al. Interleukin-6 signaling regulates hematopoietic stem cell emergence. Exp Mol Med. 2019;51:124.
83. Shen Y, Song Z, Lu X, Ma Z, Lu C, Zhang B, et al. Fas signaling-mediated TH9 cell differentiation favors bowel inflammation and antitumor functions. Nat Commun. 2019;10:2924.
84. Zhao W, Ajani JA, Sushovan G, Ochi N, Hwang R, Hafley M, et al. Galectin-3 mediates tumor cell-stroma interactions by activating pancreatic stellate cells to produce cytokines via integrin signaling. Gastroenterology. 2018;154:1524–37.e6.
85. Ladinsky MS, Araujo LP, Zhang X, Veltri J, Galan-Diez M, Soualhi S, et al. Endocytosis of commensal antigens by intestinal epithelial cells regulates mucosal T cell homeostasis. Science. 2019;363:eaat4042.
86. Wu S, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med. 2009;15:1016–22.
87. Ang QY, Alexander M, Newman JC, Tian Y, Cai J, Upadhyay V, et al. Ketogenic diets alter the gut microbiome resulting in decreased intestinal Th17 cells. Cell. 2020;181:1263–75.e16.
88. Xu C, Ruan B, Jiang Y, Xue T, Wang Z, Lu H, et al. Antibiotics-induced gut microbiota dysbiosis promotes tumor initiation via affecting APC-Th1 development in mice. Biochem Biophys Res Commun. 2017;488:418–24.
89. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science. 2013;342:967–70.
90. He Y, Fu L, Li Y, Wang W, Gong M, Zhang J, et al. Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic CD8(+) T cell immunity. Cell Metab. 2021;33:988–1000.e7.
91. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science. 2015;350:1084–9.
92. Probst HC, Muth S, Schild H. Regulation of the tolerogenic function of steady-state DCs. Eur J Immunol. 2014;44:927–33.
93. Liu K, Waskow C, Liu X, Yao K, Hoh J, Nussenzweig M. Origin of dendritic cells in peripheral lymphoid organs of mice. Nat Immunol. 2007;8:578–83.
94. Reizis B. Plasmacytoid dendritic cells: development, regulation, and function. Immunity. 2019;50:37–50.
95. Schaupp L, Muth S, Rogell L, Kofoed-Branzk M, Melchior F, Lienenklaus S, et al. Microbiota-Induced Type I interferons instruct a poised basal state of dendritic cells. Cell. 2020;181:1080–96.e19.
96. Durant L, Stentz R, Noble A, Brooks J, Gicheva N, Reddi D, et al. Bacteroides thetaiotaomicron-derived outer membrane vesicles promote regulatory dendritic cell responses in health but not in inflammatory bowel disease. Microbiome. 2020;8:88.
97. Bessman NJ, Mathieu JRR, Renassia C, Zhou L, Fung TC, Fernandez KC, et al. Dendritic cell-derived hepcidin sequesters iron from the microbiota to promote mucosal healing. Science. 2020;368:186–9.
98. Uribe-Herranz M, Rafail S, Beghi S, Gil-de-Gómez L, Verginadis I, Bittinger K, et al. Gut microbiota modulate dendritic cell antigen presentation and radiotherapy-induced antitumor immune response. J Clin Invest. 2020;130:466–79.
99. Mayoux M, Roller A, Pulko V, Sammicheli S, Chen S, Sum E, et al. Dendritic cells dictate responses to PD-L1 blockade cancer immunotherapy. Sci Transl Med. 2020;12:eaav7431.
100. Suzuki T. Regulation of intestinal epithelial permeability by tight junctions. Cell Mol Life Sci. 2013;70:631–59.
101. Wan C, Sun Y, Tian Y, Lu L, Dai X, Meng J, et al. Irradiated tumor cell-derived microparticles mediate tumor eradication via cell killing and immune reprogramming. Sci Adv. 2020;6(13):eaay9789.
102. Wang X, Allen TD, May RJ, Lightfoot S, Houchen CW, Huycke MM. Enterococcus faecalis induces aneuploidy and tetraploidy in colonic epithelial cells through a bystander effect. Cancer Res. 2008;68:9909–17.
103. Yang Y, Wang X, Huycke T, Moore DR, Lightfoot SA, Huycke MM. Colon macrophages polarized by commensal bacteria cause colitis and cancer through the bystander effect. Transl Oncol. 2013;6:596–606.
104. Wang X, Yang Y, Huycke MM. Commensal bacteria drive endogenous transformation and tumour stem cell marker expression through a bystander effect. Gut. 2015;64:459–68.
105. Wang X, Yang Y, Huycke MM. Commensal-infected macrophages induce dedifferentiation and reprogramming of epithelial cells during colorectal carcinogenesis. Oncotarget. 2017;8:102176–90.
106. Sethi V, Kurtom S, Tarique M, Lavania S, Malchiodi Z, Hellmund L, et al. Gut microbiota promotes tumor growth in mice by modulating immune response. Gastroenterology. 2018;155:33–7.e6.
107. Chen ZF, Ai LY, Wang JL, Ren LL, Yu YN, Xu J, et al. Probiotics Clostridium butyricum and Bacillus subtilis ameliorate intestinal tumorigenesis. Future Microbiol. 2015;10:1433–45.
108. Overacre-Delgoffe AE, Cillo AR, Bumgarner HJ, Burr AHP, Tometich JT, Bhattacharjee A, et al. Microbiome-specific T follicular helper cells drive tertiary lymphoid structures and anti-tumor immunity against colorectal cancer. bioRxiv. 2021.

109. Eaton K, Pirani A, Snitkin ES. Replication Study: Intestinal inflammation targets cancer-inducing activity of the microbiota. eLife. 2018;7:34364.
110. Li Y, Tinoco R, Elmen L, Segota I, Xian Y, Fujita Y, et al. Gut microbiota dependent anti-tumor immunity restricts melanoma growth in Rnf5(-/-) mice. Nat Commun. 2019;10:1492.
111. Fox JG, Feng Y, Theve EJ, Raczynski AR, Fiala JL, Doernte AL, et al. Gut microbes define liver cancer risk in mice exposed to chemical and viral transgenic hepatocarcinogens. Gut. 2010;59:88–97.
112. Bertocchi A, Carloni S, Ravenda PS, Bertalot G, Spadoni I, Lo Cascio A, et al. Gut vascular barrier impairment leads to intestinal bacteria dissemination and colorectal cancer metastasis to liver. Cancer Cell. 2021;39:708–24.e11.
113. Kwon SJ, Lee GT, Lee JH, Iwakura Y, Kim WJ, Kim IY. Mechanism of pro-tumorigenic effect of BMP-6: neovascularization involving tumor-associated macrophages and IL-1a. Prostate. 2014;74:121–33.
114. Mu HQ, He YH, Wang SB, Yang S, Wang YJ, Nan CJ, et al. MiR-130b/TNF-alpha/NF-kappaB/VEGFA loop inhibits prostate cancer angiogenesis. Clin Transl Oncol. 2019;22(1):111–21.
115. Poutahidis T, Cappelle K, Levkovich T, Lee CW, Doulberis M, Ge Z, et al. Pathogenic intestinal bacteria enhance prostate cancer development via systemic activation of immune cells in mice. PLoS One. 2013;8:e73933.
116. Royuela M, Rodriguez-Berriguete G, Fraile B, Paniagua R. TNF-alpha/IL-1/NF-kappaB transduction pathway in human cancer prostate. Histol Histopathol. 2008;23:1279–90.
117. Calcinotto A, Brevi A, Chesi M, Ferrarese R, Garcia Perez L, Grioni M, et al. Microbiota-driven interleukin-17-producing cells and eosinophils synergize to accelerate multiple myeloma progression. Nat Commun. 2018;9:4832.
118. Daisley BA, Chanyi RM, Abdur-Rashid K, Al KF, Gibbons S, Chmiel JA, et al. Abiraterone acetate preferentially enriches for the gut commensal Akkermansia muciniphila in castrate-resistant prostate cancer patients. Nat Commun. 2020;11:4822.
119. Inaguma S, Lasota J, Czapiewski P, Langfort R, Rys J, Szpor J, et al. CD70 expression correlates with a worse prognosis in malignant pleural mesothelioma patients via immune evasion and enhanced invasiveness. J Pathol. 2020;250(2):205–16.
120. Esfahani K, Al-Aubodah TA, Thebault P, Lapointe R, Hudson M, Johnson NA, et al. Targeting the mTOR pathway uncouples the efficacy and toxicity of PD-1 blockade in renal transplantation. Nat Commun. 2019;10:4712.
121. Shi L, Sheng J, Wang M, Luo H, Zhu J, Zhang B, et al. Combination therapy of TGF-β blockade and commensal-derived probiotics provides enhanced antitumor immune response and tumor suppression. Theranostics. 2019;9:4115–29.
122. Repass J, Maherali N, Owen K. Registered report: Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Elife. 2016;5:10012.
123. Yu T, Guo F, Yu Y, Sun T, Ma D, Han J, et al. Fusobacterium nucleatum promotes chemoresistance to colorectal cancer by modulating autophagy. Cell. 2017;170:548–63.e16.
124. Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Science. 2017;357:1156–60.
125. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillere R, Hannani D, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science. 2013;342:971–6.
126. Fink LN, Zeuthen LH, Ferlazzo G, Frokiaer H. Human antigen-presenting cells respond differently to gut-derived probiotic bacteria but mediate similar strain-dependent NK and T cell activation. FEMS Immunol Med Microbiol. 2007;51:535–46.
127. Probst HC, McCoy K, Okazaki T, Honjo T, van den Broek M. Resting dendritic cells induce peripheral CD8+ T cell tolerance through PD-1 and CTLA-4. Nat Immunol. 2005;6:280–6.
128. Wei SC, Sharma R, Anang NAS, Levine JH, Zhao Y, Mancuso JJ, et al. Negative Co-stimulation constrains T cell differentiation by imposing boundaries on possible cell states. Immunity. 2019;50:1084–98.e10.
129. Lau J, Cheung J, Navarro A, Lianoglou S, Haley B, Totpal K, et al. Tumour and host cell PD-L1 is required to mediate suppression of anti-tumour immunity in mice. Nat Commun. 2017;8:14572.
130. Wei SC, Levine JH, Cogdill AP, Zhao Y, Anang NAS, Andrews MC, et al. Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. Cell. 2017;170:1120–33.e17.
131. Vetizou M, Pitt JM, Daillere R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science. 2015;350:1079–84.
132. Gros A, Tran E, Parkhurst MR, Ilyas S, Pasetto A, Groh EM, et al. Recognition of human gastrointestinal cancer neoantigens by circulating PD-1+ lymphocytes. J Clin Invest. 2019;129(11):4992–5004.
133. Ribas A, Dummer R, Puzanov I, VanderWalde A, Andtbacka RHI, Michielin O, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 Immunotherapy. Cell. 2017;170:1109–19.e10.
134. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillere R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018;359:91–7.
135. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359:97–103.
136. Jin Y, Dong H, Xia L, Yang Y, Zhu Y, Shen Y, et al. The diversity of gut microbiome is associated with favorable responses to anti-programmed death 1 immunotherapy in Chinese patients with NSCLC. J Thorac Oncol. 2019;14:1378–89.
137. Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science. 2018;359:104–8.
138. Shi L, Sheng J, Wang M, Luo H, Zhu J, Zhang B, et al. Combination therapy of TGF-beta blockade and commensal-derived probiotics provides enhanced antitumor immune response and tumor suppression. Theranostics. 2019;9:4115–29.

How to cite this article: Yang X, Guo Y, Chen C, Shao B, Zhao L, Zhou Q, et al. Interaction between intestinal microbiota and tumour immunity in the tumour microenvironment. Immunology. 2021;164:476–493. https://doi.org/10.1111/imm.13397