Gut Microbiota and Antitumor Immunity: Potential Mechanisms for Clinical Effect

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ABSTRACT

Several landmark preclinical studies have shown an association between the gut microbiota and the effectiveness of immunotherapy for cancer. These studies have sparked clinical trials aimed at modulating the gut microbiota in order to improve clinical response rates to immunotherapy. Despite this, the mechanisms through which the gut microbiota influences the effectiveness of immunotherapy are still incompletely characterized. Preclinical and preliminary clinical findings from numerous types of gut microbiota modulation studies, including fecal transplantation, probiotics, consortia, and diet, demonstrate that favorable microbiota modulation is associated with increased intratumoral infiltration of $CD8^+$ effector T cells. This $CD8^+$ T-cell infiltration is often associated with enhanced intratumoral activity of T-helper type 1 cells and dendritic cells and a lower density of immunosuppressive cells. Herein, we discuss how gut microbiota may affect the activity of immune cells by at least three interlacing mechanisms: activation of pattern recognition receptors, molecular mimicry, and impact of metabolites. We also discuss the therapeutic potential and limitations of the different gut microbiota modulation techniques and their putative mechanisms of immune activation.

Introduction

A series of landmark studies have been published demonstrating associations between the composition of the gut microbiota and clinical response to cancer immunotherapy (1–3). In addition, the use of antibiotics by patients with cancer prior to starting immune checkpoint blockade (ICB) immunotherapy has been associated with adverse prognosis (3, 4), and strategies to manipulate gut microbiota to improve immunotherapy responses are currently being tested in clinical trials. Although the notion that gut microbiota can influence immunity is well established (5), the specific mechanisms through which the microbiota affects immunity and responses to cancer immunotherapy are still being elucidated. Here, we review the current evidence on how gut microbiota affects antitumoral immune activity. We also discuss the impact of gut microbiota modulation strategies on immunity and immunotherapy response with a summary of ongoing efforts.

Gut Microbiota Shapes Antitumoral Immunity

The antitumor immune response is highly complex and involves multiple key players (6). Antigen-presenting cells can infiltrate tumors and present antigens to lymphocytes in the tumor microenvironment (7, 8) or in tumor-draining lymph nodes. Antigen recognition leads to activation of $CD4^+$ T-helper type 1 (Th1) cells and $CD8^+$ T cells and also counters activation of $CD4^+$ T regulatory cells (T_{reg}) and myeloid-derived suppressor cells (MDSC). Evidence that gut microbiota can affect the differentiation and activation of each of these cell types comes from studies in germ-free (GF) mice and mice treated with antibiotics, as discussed below. Some of the mechanisms through which gut microbiota can induce immune modulation include activation of pattern recognition receptors (PRR), antigen-specific activation, and metabolite-derived modulation (**Fig. 1**).

Activation of PRRs

GF mice and mice treated with broad-spectrum antibiotics have a reduced frequency of hematopoietic stem and progenitor cells in the bone marrow (9). Interestingly, immune progenitor activity can be restored in GF mice by administration of lipopolysaccharide (LPS), sterile-filtered and boiled serum, or autoclaved cecal content from specific pathogen–free mice (10). The bacterial particles activate PRRs such as MyD88-dependent Toll-like receptors (TLR) and nucleotide-binding oligomerization domain-containing proteins (NOD; ref. 11). These PRRs are expressed by mesenchymal stromal cells in the bone marrow, and their activity is STAT1 dependent. Upon PRR activation, the stromal cells secrete growth factors that support hematopoietic stem and progenitor cell proliferation and thus enhance hematopoiesis.

GF mice have also reduced $CD8^+$ T-cell thymic maturation, and administration of bacterial peptidoglycans, which are sensed by thymocyte NOD receptors, promotes $CD8^+$ T-cell maturation in these animals (12). Similar findings were reported in a study in which female mice were treated with antibiotics during the final stages of pregnancy and throughout the lactation period. Infant mice from these litters were highly susceptible to viral infections, and immune-profiling studies demonstrated that $CD8^+$ T cells were unable to sustain IFNγ production upon activation due to impaired downstream signaling of T-cell receptors (TCR). Oral administration of LPS to the infant mice was associated with increased signaling of TLR4–MyD88 in $CD8^+$ T cells, which restored their ability to produce IFNγ compared with control mice and prolonged survival in the context of an induced systemic viral infection (13).

The gut microbiota is composed not only of bacteria, but also of viruses, protozoa, and fungi that may positively or negatively affect

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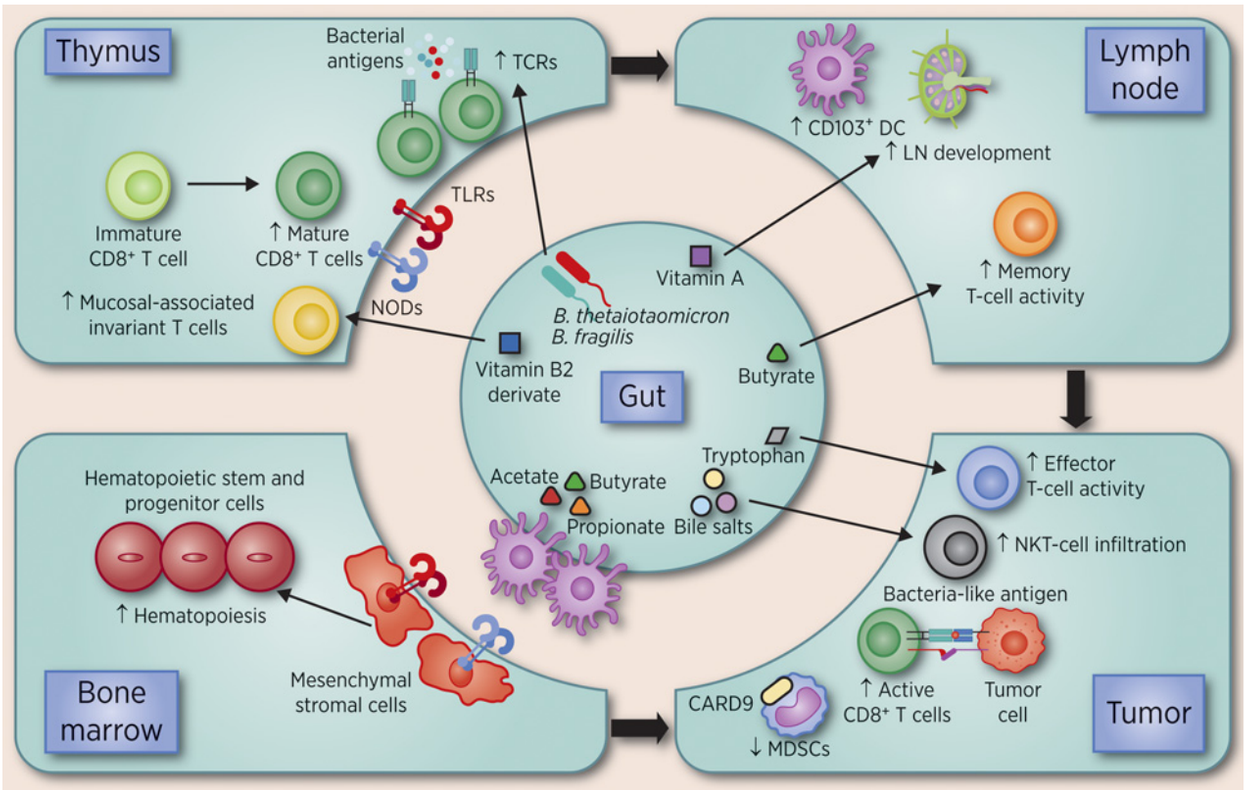

Figure 1.

Mechanisms of immune modulation by the gut microbiota. The gut microbiota may affect immune cells playing key roles in antitumoral immunity. The microbiota may affect maturation processes, either in the bone marrow [for dendritic cells (DC)] or in the thymus (for T cells). Microbiota may also affect the activity of mature immune cells within the tumor microenvironment or in the surrounding lymph nodes. The microbiota-derived effect is mediated by three potential pathways: activation of pathogen recognition receptors such as TLRs and NODs; molecular mimicry initiating immune responses against cancer antigens that are similar to bacterial ones; and metabolic modulation using vitamins, short-chain fatty acids, bile salt, or amino acids that promote favorable intracellular processes among host cells. LN, lymph node; NOD, nucleotide-binding oligomerization domain-containing proteins; TCR, T-cell receptor; TLR, Toll-like receptor.

immunity and antitumor immune responses. These are less well studied in the context of shaping antitumor immunity, as many of the early studies published on this subject utilized 16S rRNA gene sequencing, which captures only bacterial signatures, rather than metagenomic sequencing, which captures additional signature from viruses, fungi, and protists. Nonetheless, some evidence exists regarding the impact of nonbacterial microbiota on antitumor immunity, with intratumoral fungi promoting pancreatic cancer progression (14). This relationship is further highlighted by a study using mice deficient in caspase recruitment domain family member 9 (CARD9), which is an adaptor protein in macrophages that plays a key role in antifungal immune activity. *CARD9*$^{-/-}$ mice were found to have abnormally high relative abundance of fungi in their gut microbiota compared with wild-type mice, particularly *Candida tropicalis*. In addition, the *CARD9*$^{-/-}$ mice had a higher colon tumor burden (15), and the tumors were characterized by upregulation of IL6, IL10, and TGFß. Fecal microbiota transplant (FMT) from *CARD9*$^{-/-}$ mice into GF mice caused a similar pattern of tumorigenesis with a significant expansion in the number of MDSCs in the colon.

Molecular mimicry

In addition to activating PRRs, gut microbiota may induce antigen-specific immune responses. The mechanism for this antigen-specific activation is a cross-reaction between a bacterial antigen and a human protein containing similar antigenic sequences. This phenomenon is known as molecular mimicry. In a murine model of type 1 diabetes mellitus, CD8$^+$ T cells harboring TCRs specific for islet-specific glucose-6-phosphatase catalytic subunit–related protein (IGRP) can be activated by peptides from oral and gut bacteria that have proteins that share strong homology with IGRP (16). Certain *Bacteroides* species contain peptides that mimic myosin heavy chain 6 protein, which is expressed by cardiac myocytes. *Bacteroides thetaiotaomicron*–activated Th1 and Th17 cells have been reported to have a key role in lethal inflammatory cardiomyopathy in mice, and this was abrogated in GF mice and could be mitigated by antibiotic therapy (17).

Antigenic mimicry may also indirectly regulate maturation of immune cells, as plasmacytoid dendritic cells (DC) activated by the polysaccharide A component of *Bacteroides fragilis* were shown to migrate from the mouse colon to the thymus and promote maturation of PLZF$^+$ lymphocytes (18). Similarly, immune responses associated with antigenic mimicry have recently been demonstrated in preclinical models of cancer. The tail length tape measure protein (TMP) of a bacteriophage found in *Enterococcus hirae* contains MHC class I binding epitopes, and mice bearing the *E. hirae* bacteriophage developed anti-TMP T-cell clones that could cross-react against melanoma cells (19). In preclinical models, administration of TMP-containing

enterococci enhanced antitumoral T-cell activity and overall effectiveness of anti–PD-1 ICB. T-cell clones targeting the *Bifidobacterium breve* antigen SVYRYYGL also have been shown to cross-react against melanoma cells (20).

Preliminary evidence for microbiota-derived molecular mimicry has also been reported in humans. The presence of TMP-containing enterococci phage in patient stool was associated with improved clinical response to anti–PD-1 therapy in patients with kidney and lung cancer (19). In addition, studies in pancreatic cancer comparing long-term with short-term survivors demonstrated that in long-term survivors, the tumor microenvironment is characterized by a higher density of neoantigens that are similar to microbially derived epitopes and an enhanced $CD8^+$ T-cell infiltration (21, 22). Importantly, FMT using fecal samples from long-term survivors of pancreatic cancer into GF mice conferred enhanced antitumor immunity and tumor control compared with FMT using fecal samples from short-term survivors and FMT from healthy controls (22).

Immunomodulation via microbially derived metabolites

One of the most provocative mechanisms by which gut microbiota may mediate immunomodulation is via production of metabolites. GF mice have underdeveloped lymphoid organs throughout their body, even in remote, nongastrointestinal sites of the body (23). This is at least partially related to the influence of microbes on DCs, as investigators have demonstrated that intravenous administration of microbiota-activated $CD103^+$ DCs into GF mice restores the cellularity and structure of the peripheral lymph nodes via a vitamin A–dependent process (24).

The gut microbiota can generate metabolites from naturally occurring compounds in the gut. For example, a riboflavin (vitamin B2) derivate called 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil can rapidly cross the gut mucosa and enter the bloodstream, through which it can travel to the thymus, where it induces the expansion of mucosal-associated invariant T cells, which are lymphocytes that are absent in GF mice (25). Bile acids are also potential sources of microbially derived immunomodulators because gram-positive bacteria in the gut metabolize primary bile acids into secondary ones with different properties. Reabsorption of primary bile acids in the gut increases expression of CXCL16 in liver endothelial cells, which attracts $CXCR6^+$ natural killer T (NKT) cells. Liver $CXCR6^+$ NKT accumulation can inhibit tumor growth. Such accumulation was demonstrated to be bile acid–dependent in mice, as antibiotic depletion of gut gram-positive bacteria increased the number of liver $CXCR6^+$ NKT cells, whereas feeding with secondary bile acids decreased this cell population (26).

Certain foods have been studied for their potential role in improving immunity. Plants like parsley and berries contain flavonoids, which can be degraded by the gut microbiota to desaminotyrosine (DAT). DAT has been demonstrated to protect mice from influenza virus infection by enhancing type I IFN signaling (27). Dietary fiber is one of the most studied immunomodulatory foods. Dietary fibers cannot be directly digested by humans for use as an energy source, rather they are fermented by certain gut bacteria into short-chain fatty acids (SCFA), which can then be used by as an energy source. Higher levels of fecal SCFA have been associated with improved clinical response to anti–PD-1 ICB in patients with advanced cancer (28). A high fiber diet and increased SCFA production may also be associated with increased $CD103^+$ DC production in the bone marrow, increased phagocytic capacity of DCs in the lungs and gut, and dampened DC-mediated Th2 responses (29, 30). Bachem and colleagues reported that antigen-activated $CD8^+$ T cells that were transferred into GF mice failed to transition into long-lived memory cells (31). The SCFA butyrate enhanced the memory potential of activated $CD8^+$ T cells by promoting oxidative phosphorylation and mitochondrial function in the T cells. This finding may have relevance in cancer immunotherapy, as mitochondrial metabolism and oxidative phosphorylation proteomic pathways are enriched in tumor samples of patients with metastatic melanoma who respond to anti–PD-1 ICB and adoptive cell therapies (32), although this needs to be further evaluated.

Another example of the tangentiality between microbiota functional activity, diet, and the tumor microenvironment is the essential amino acid tryptophan. Tryptophan can be metabolized by the gut microbiota to serotonin, kynurenine, or indoles, which are aryl hydrocarbon receptor (AhR) agonists (33). Indoles can cross the gut–blood barrier, and then, after traveling through the bloodstream, cross the blood–brain barrier to activate astrocytes and induce immunosuppression in the brain. In a murine experimental autoimmune encephalomyelitis model, central nervous system inflammation was decreased when mice were treated with a tryptophan-rich diet but increased when the mice were treated with antibiotics (34). This may be clinically relevant as patients with multiple sclerosis have low circulating levels of tryptophan-derived metabolites (34). Kynurenine, which is also an AhR agonist, can suppress NKT cell and DC activity, arresting T-cell proliferation and inducing T-cell apoptosis (35). It is a potent immunosuppressor, and tryptophan catabolism to kynurenine by indoleamine 2,3-dioxygenase (IDO)-1 is one of the reasons that IDO-1 is known as a key immune checkpoint in the tumor microenvironment and is a therapeutic target in ongoing cancer clinical trials (36).

Together, these data serve as an example of the delicate equilibrium between the gut microbiota and host immune activity. However, in cancer immunity, systemic effects on the immune system must be taken in the context of those effects on the tumor. A microbiota-derived metabolite, gallic acid (a type of phenolic acid), has been demonstrated to modify the tumor-suppressor activity of p53 within tumor cells and promote tumor growth (37). Hence, modulation of the microbiota may represent a tractable strategy to improve antitumor immunity and responses to immunotherapy by acting in multiple ways, on both immune and tumor cells.

The Immune Effect of Gut Microbiota Modulation Strategies

Based on data from preclinical studies and human cohorts suggesting that gut microbiota affects responses to cancer therapy, numerous trials are now underway to test different approaches to modulating gut microbiota. Each of these approaches differs substantially, and the mechanisms through which they may affect antitumor immune responses must be carefully considered, but much is still unknown.

Fecal microbial transplantation

FMT involves the transfer of fecal material from an identified donor to a recipient. Samples are prepared by sieve or filtration with reconstitution in a liquid form so it can be either infused via endoscopy or packaged and stored in stool capsules for oral ingestion (38). Due to these minimal preparation steps, most of the donor fecal content, including bacteria, viruses, fungi, microbial particles, and metabolites, are preserved and can be transferred to the recipient. FMT has been used for decades as a therapy for recurrent or refractory *Clostridioides difficile* colitis. However, FMT is just beginning to be studied in the

context of cancer. Several preclinical studies have shown that FMT using feces from patients with cancer who have responded to immunotherapy enhances the effectiveness of both anti–PD-1 and anti–CTLA-4 therapies in GF mice and mice treated with antibiotics, compared with FMT using nonresponder feces (1–3, 39). These FMT-enhanced antitumor responses were associated with, and probably mediated by, an intratumoral immune microenvironment in which there is increased infiltration of $CXCR3^+CD4^+$ (Th1-related) T cells and IFNγ-producing cytotoxic $CD8^+$ T cells and decreased infiltration of $ROR\gamma^+$ Th17 cells and $CD11b^+CD11c^+$ suppressive myeloid cells.

One of the most intriguing characteristics of FMT is its potential dual utility in patients with cancer; although it can boost antitumor immune responses, it can also suppress immunotherapy-related colitis (40). A reduction in $CD8^+$ T-cell density and an increase of $FoxP3^+$ T_{reg} within the colonic mucosa have been seen from pre- to posttreatment colonic biopsies after patients with cancer were given healthy-donor FMT. This report only had data from a few patients, and therefore, no conclusions could be made regarding putative microbial taxa that may have contributed to therapeutic response. However, the therapeutic benefit may have been in part related to the transfer of a more diverse gut microbiome with functional redundancy. Consistent with this, other investigators have noted that low microbial diversity within the gut microbiome is associated with an increased rate of severe immune-related adverse events (irAE) and lack of response to treatment with combination anti–CTLA-4 and anti–PD-1 ICB (41).

To date, several clinical trials are assessing whether adding FMT to immunotherapy can improve outcomes for patients with various types of cancer (NCT03772899, NCT03341143, and NCT04521075). Preliminary results from one trial combining FMT and anti–PD-1 reinduction in patients with refractory metastatic melanoma demonstrated clinical responses that were associated with increased intratumoral infiltration of $CD8^+$ T cells (42). The participants also did not develop irAEs, even though they had when previously treated with immunotherapy.

Probiotics and live biotherapeutics targeting single gut microbes

In addition to FMT, the use of probiotics and live biotherapeutics targeting specific gut microbes has also been studied in the context of treatment with ICB. Increased abundance of *Akkermansia muciniphila* in the gut microbiome of patients with non–small cell lung cancer and kidney cancer was shown to be associated with enhanced response to treatment with ICB. Transfer of this microbe into the gut microbiome in preclinical models of cancer increased production of IL12 by DCs, enhanced recruitment of $CCR9^+CXCR3^+CD4^+$ T cells in epithelial tumors and lymph nodes, and improved efficacy of PD-1 ICB in treated mice (3). Other gut microbes have also been studied. *Bifidobacterium* has been found to be enriched in the gut microbiota of responding patients with metastatic melanoma being treated with anti–PD-1 ICB. Treatment with *Bifidobacterium* in preclinical models of cancer was associated with a higher density of MHC class II^{hi} DCs in melanoma tumors, increased tumor-specific $CD8^+$ T cells in the tumor microenvironment, and enhanced responses to treatment with anti–PD-1 ICB (43). Such approaches have also been studied in the context of anti–CTLA-4 ICB in preclinical models of sarcomas and colon carcinoma. In this study, treatment with enteric *B. fragilis* was associated with improved responses to anti–CTLA-4, maturation and production of IL12 by DCs, and increased T-cell memory responses (39). Several human clinical trials are underway incorporating the administration of these types of approaches in patients with cancer who will subsequently be treated with anti–PD-1 ICB (NCT03595683 and NCT03637803). Data are currently not available on the safety and efficacy of such approaches, or on their ability to stimulate robust antitumor immunity. Nonetheless, this remains a potentially viable strategy and offers less complexity and perhaps an enhanced safety profile over treatment with FMT, as pathogens are easily transmittable via FMT (42).

Gut microbial consortia

A lab-produced consortium of microbes might, in theory, incorporate a probiotic-like high safety profile and an FMT-like improved functionally, as these small microbial communities can work together. Major efforts are underway to develop consortia of microbes that can be administered via the gastrointestinal tract to enhance the function of the gut microbiota and the immunotherapy response, with several trials underway or in development (NCT03817125 and NCT04208958). These consortia have been informed by human cohort studies and preclinical models (44, 45) and contain either consortia derived from donors with what are considered to be favorable gut microbiota signatures (NCT03817125) or consortia engineered based on results from studies involving transplantation of human fecal matter into mice (45). Notably, the consortia derived from FMT studies in preclinical models demonstrated that transfer of a consortia consisting of 11 bacterial strains into the gut of tumor-bearing mice was associated with a high density of IFNγ-producing $CD8^+$ T cells, and enhanced efficacy of anti–PD-1 and anti–CTLA-4 ICB in mouse models of colon cancer and melanoma (45). Additional efforts are underway to reconstruct gut microbial consortia via culturomics and other approaches (46). However, potential complexities may exist with scalability and consistency of manufacturing of such products, as well as with regulatory aspects.

Diet and prebiotics

When contemplating strategies to modulate gut microbiota, it is important to consider other factors that affect gut microbiota, including diet and prebiotics (47). Oral intake of inosine, together with IL12 secretion by DCs, has been shown to enhance the effectiveness of anti–CTLA-4 ICB against different tumors implanted in mice by promoting antitumoral T-cell activity (48). Prebiotics are dietary compounds, such as fibers and inulin, that may support certain gut microbiota populations or modify their functionality. Administration of prebiotics has been studied across many disease types. Recent studies in preclinical cancer models suggest that administration of inulin is associated with enhanced antitumoral immune responses in melanoma (49). In these studies, mice who received treatment with prebiotics demonstrated higher intratumoral infiltration of effector IFNγ-producing $CD4^+$ and $CD8^+$ T cells, plasmacytoid DCs, and conventional $CD8\alpha^+$ DCs. Tumor-resident DCs isolated from mice treated with prebiotics expressed higher levels of MHC class I and MHC class II. Importantly, all of the effects of prebiotics on antitumor immunity and tumor growth were dependent on the gut microbiota, as GF mice failed to demonstrate these changes (49). A few clinical trials assessing the potential effect of dietary modifications and prebiotics in patients with metastatic cancer undergoing immunotherapy are currently underway (NCT04552418 and NCT04316520).

Conclusions

There is increasing interest in targeting gut microbiota to enhance immunity and immunotherapy response; however, optimal strategies

to do so are incompletely understood. Critical insights are being gained into the mechanisms through which gut microbiota modulates immunity and will help refine strategies to target gut microbiota in cancer and other states of health and disease.

Authors' Disclosures

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