Recent Advancements in Microbiome–Immune Homeostasis and their Involvement in Cancer Immunotherapy

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Abstract

The microbial genome of bacteria, archaea, protists, fungi, and viruses which colonize in humans is known as the microbiome. The population of microbes in the human body is known as microbiota, its composition may differ with concerning host factors like sex, age, obesity, physical inactivity, alcohol consumption, smoking, diet, and polymorphisms in dominant human oncogenes. The current chapter is ascertaining the connection between microbiota and cancer, the role of the microbiota in cancer immunotherapy, which leads to significant advances and scope in the etiology of cancer. Different processes are studied and have been promising to conclude the role of microbiota in tumorigenesis and progression, processes like genotoxicity, induction of chronic inflammation, bacteria-mediated cell proliferation, and activation of procarcinogens show the interference of microbiota with the tumors. More research studies must focus on microbiota interaction with the host to define its contribution to the growth and development of cancers and identify microbiome as a potential cancer marker and develop personalized medicine to treat malignancies. This chapter outlines various researches, explaining how the microbiota itself enclose a novel paradigm in the prevention of cancer and its management. Paramount to develop microbiota-based immunotherapy for treating cancer, few challenges in microbiome research are to identify individual microbial species such as viruses, protozoans, archaea, protists, and fungi that causally affect cancer phenotypes and unravel the underlying mechanisms. Here, we discuss a few relevant technologies and few

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P. V. Bramhachari (ed.), *Microbiome in Human Health and Disease*,
https://doi.org/10.1007/978-981-16-3156-6_12

challenges in studying the microbiome and their involvement in cancer immunotherapy.

Keywords

Microbiome · Immunotherapy · Carcinogenesis · Epidemiology · CTLA-4 Cytotoxic T-lymphocyte Antigen-4

12.1 Introduction

The human microbiota, collective of primary bacteria and other microbes, like archaea, fungi, protozoa, protozoan viruses, helminthic worms that reside in the human body, the genetic material of microbiota is known as the microbiome. It is an inhabitant in the human body, within the surface of the epithelial barrier, 99% occupied in the gut and 1% in skin, vagina, nasal, and mouth. The fluctuation of the equilibrium, which is detrimental due to the loss of beneficial microorganisms, is known as dysbiosis. Physiology factors, lifestyle changes in the diet all affect the health of microbiomes in the host. This dysbiosis causes inflammation in epithelial cells and is known to cause tumor development. There are corrective treatments for dysbiosis mentioned in this chapter, which showed promising results in the microbiome caused by diseases. Moreover, multiple techniques and models used in the characterization of microbes are discussed briefly in this chapter.

The gut microbiome has shown significant importance in immune cell development and maintains equilibrium with commensal microbes. These microbes have regulatory roles in the development of mucosal immune systems. Intestinal microbes produce short-chain fatty acids, which play a crucial role in tumor prevention and activation for apoptosis. Besides, they have an impact on efficacy immunotherapy in cancer patients by blocking cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death ligand 1 (PD-L1), which is explained below in detail (Temraz et al. 2019).

12.2 Microbiome

The Human Microbiome Research observed 11,174 primary biological specimens in a study conducted in 242 healthy adults (Methé et al. 2012). The microbiota has a considerable impact on the host's immunity, physiological functions, particularly metabolism, cognitive and neurological function, inflammation, hematopoiesis (Roy and Trinchieri 2017). The microbiome is first acquired by vertical transmission from mothers during delivery and lactation period. Newborns birth by cesarean has abundant skin microbiota of mothers compared to birth by vaginal delivery, later possess more maternal vaginal microbiota (Dominguez-Bello et al. 2016). Total microbial counts about ten times more than the human cells, with more genes, concerning the human genome (Shahanavaj et al. 2015). Primarily dominant bacteria

found in the healthy human gut are *Bacteroidetes* and *Firmicutes;* their percentage range varies from 10% to 90% (Allaband et al. 2019). Some research studies detailed, secretions by the bacteria make it dominant in the interbacterial competition with a high population of *B. fragilis* strain (Garud and Pollard 2020). Microbiota of the gut is known as the "second genome" as it shows a significant impact on the internal activities of the host; thus, it is also called "forgotten organ." The gastrointestinal microbiome has been observed to have a crucial effect on overall health and serves as the best model to understand microbiota and host interactions (Schwabe and Jobin 2013).

Gut bacteria is categorized into three types based on their function in the host:

- *Symbionts*: (90% in the gut) Microbes in mutualistic benefit to the host.
- *Conditioned Pathobionts*: Usually harmless, causes disease in unfavorable condition.
- *Pathobionts*: Disease-causing microorganisms.

The pathobionts can be harmful when there is a disturbance in equilibrium between the gut microbiota and the host due to altered dietary habits, exposure of pathogens, the action of antibiotics, and other environmental factors like change of weather or disturbance in the circadian clock. Alterations in the homeostasis in the microbial communities are known as "dysbiosis" (Helmink et al. 2019a). It is affected by the physiological and pathological changes that take place in the host (Shui et al. 2020). Some recent finding suggests colorectal cancer (CRC), inflammatory bowel disease (IBD), celiac disease, obesity may have been caused by pathobionts. Dysbiosis leads to a leaky gut by exposure to pathogens, increasing the intestinal permeability, promoting translocation of gut bacteria, and dysplasia of the immune system affecting the homeostasis of the gut (Zhou et al. 2020). To treat the above condition caused by dysbiosis through fecal microbiota transplantation (FMT) and other novel therapies can be introduced. Gut microbiome study is in a preliminary stage of the investigation to know the functional properties of commensal bacteria, and its mechanism involved to interact with the host is not completely understood. Moreover, multiple promising types of research have suggested gut microbiota showcase great potential towards medical treatments of cancer and other diseases (Kho and Lal 2018).

12.2.1 Esophageal Microbiota

The esophageal microbiome has been studied in healthy and diseased conditions with the help of recent gene sequencing tools. It is observed that a healthy human esophagus contains abundant *Streptococcus* (gram +ve), compared to the infected esophagus, with a high amount of gram-negative bacteria (Rajagopala et al. 2017). Microorganisms inhabiting the esophagus are *Bacteroidetes, fusobacteria, proteobacteria,* and *spirochetes*. These microbes produce lipopolysaccharides (LPS), which acts as an immune-activating agent in stimulating innate immune

responses that can directly treat malignancies. LPS interact with the innate immune system by binding to toll-like receptor-4 (TLR4), resulting in the activation of nuclear factor kappa B (NF-κB). High levels of NF-κB are observed in esophageal adenocarcinoma patients cascading levels of inflammatory cytokines like IL-1b, Il-6, IL-8, and TNF-a. In some research studies in mice, LPS prolongs the time of gastric emptying, which helps in increased gastric reflux to the esophagus. Therefore, using NF-κB host cell pathway inhibitors, probiotics, antibiotics, and microbiome in the esophagus can prevent cancer development (Shahanavaj et al. 2015). Some detailed studies are required to find the target in different diseases in the esophagus, diagnosing, therapeutics, and prevention (Lv et al. 2019).

12.3 Healthy and the Unhealthy Microbiome

12.3.1 Healthy Microbiome

Characterization of microbes as healthy and unhealthy is necessary to understand their functions and their roles in healthy and diseased conditions are critical. The gut microbiota is diverse compared to other host sites; a healthy microbiome considered in one host may not be healthy for others. Although there have been some patterns found in a study conducted in patients from different zones. Healthy hosts have rich microbiota, which harbors 1000 species of bacteria belonging to *Firmicutes* and *Bacteroidetes*. Different proposals from researchers say that a host with favorable gut microbiota has elicited an immune response against cancers due to antigen presentation and enhanced T cell function. Research studies in mice explain T cell response is defined for *B. fragilis or B. thetaiotaomicron* in microbiota promoting CTL-4 blockade seen in patients. Gopalakrishnan found responses to anti-PD-1 in skin cancer affected by gut microbiota by changing CD4+ IL-17+ cells and CD4+ FoxP3 + T cells. Restoring the efficacy of anti-PD-1 through T cells recruitment by *Akkermansia* in the gut microbiota sensitizing the cancer cells was studied (Chen et al. 2020). *Bacillus polyfermenticus*, a probiotic bacterium observed to affect the development of colon cancer cells by obstructing receptors like ErbB2 and ErbB3 by immune suppression, chronic inflammation, immune evasion (Shahanavaj et al. 2015). Moreover, probiotics destroying hepatocellular carcinoma is through SCFA production (Zhou et al. 2020).

Symbionts inhabiting the gut of the host play role of cancer transforming agents in distal and local carcinogenesis and involve indirectly causing induction of inflammation and immune suppression. Due to disturbed equilibrium, some microbes tend to act as a part of an unhealthy microbiome being involved in altering host physiology and metabolism (Li et al. 2019).

12.3.2 Unhealthy Microbiome

The gut microbiota of the host affects its immune system indirectly by suppressing and inducing inflammation leading to cancer development (Li et al. 2019). Few observed that some bacteria promote chronic inflammation to activate macrophages, increase reactive oxygen species (ROS) generation leading to DNA breakage and mutations (Zhou et al. 2020). Obesity leads to dysbiosis with a high volume of Clostridia, which produces secondary bile acid, deoxycholic acid (DCA) and promotes hepatic cellular carcinoma (HCC) (Schwabe and Jobin 2013).

Human tissues tightly regulate growth and death promoting signals to maintain homeostatic cell densities, tissue function, and architecture of the tissue or organ. Disruption in these signals results in uncontrolled cellular proliferation. E-cadherin and intercellular adhesion molecule have been a target for the intestinal bacteria to promote epithelial cell proliferation by activation of Wnt/u-catenin pathway (Fulbright et al. 2017).

Cyclophosphamide was found effective in translocation of the *Enterococcus hirae* small intestine bacteria to spleen and colonization of *Barnesiella intestinihominis* in the colon of the host; these microbes together contribute to the antitumor immunity (Li et al. 2019). Some examples of an unhealthy and healthy microbiota, affecting the physiological and metabolic activities of the host are listed in Fig. 12.1.

12.4 Techniques and Tools for Microbiome Analysis

Gut microbiota is well understood in recent years with the help of advanced gene sequencing tools and humanized gnotobiotic models (Kho and Lal 2018). These advanced sequencing tools have helped researchers to generate millions of sequences to study different microbial communities. Conventional techniques used to unravel the gut microbiome are 16S ribosomal RNA, metabolic characterization of the microbiome, gene amplicon sequencing, shotgun, single-cell RNA sequencing by CRISPR–Cas technology, metagenomic sequencing (Elinav et al. 2019), and next-generation sequencing tools. Of all, the composition of host–microbiota can be defined by 16S RNA ribosome amplicon sequencing and whole-genome shotgun (WGS) sequencing. Through WGS appropriate detection of the species, strains with diversity within the samples can be determined, which are concluded in 16S rRNA amplicon sequencing. The primary disadvantage of 16SrRNA sequencing is it lacks taxonomic resolution. In either case, microorganism DNA sequence samples are studied by next-generation sequencing technologies in comparison with known database sequences to analyze the presence and abundance of taxa (Saus et al. 2019). Microbial community analysis can be achieved with genomic databases and tools such as the quantitative insights into microbial ecology (QIIME), ribosomal database project (RDP) pyrosequencing, procrustes analysis, taxonomy, and ecology of ribosomal sequences (W.A.T.E.R.S) (Ursell et al. 2012).

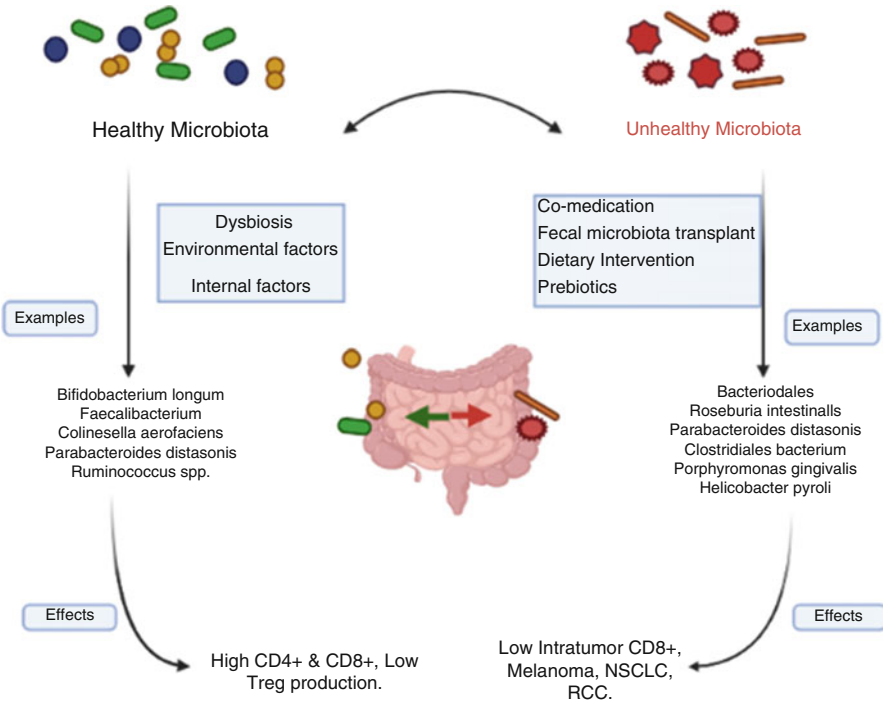

Fig. 12.1 Healthy and unhealthy microbiota inhabiting host: Different factors like dysbiosis, internal and external factors of host result in loss of healthy microbiota leading to unhealthy or harmful microbiota promoting uncontrolled cell proliferation and other clinical disorders

Human-compatible preclinical models, humanizing mice, organ-chips, and human-derived organoids are used in the study of gut microbiota and their reactions to other tissues. Fecal transplant trials have been conducted in patients, to unwrap the composition of essential microorganisms to help in immunotherapy for cancers (Elinav et al. 2019). Advanced tools and genomic database consortium are most popularly used to identify bacteria and study their effects on the host. Standardization in this research study helps to compare the various preclinical and clinical studies and understand how microbiota with different genomes have been involved in the development of malignancies.

12.5 Microbiome Therapies

The microbiota damaged due to antibiotics, drugs, changes in diet, and dysbiosis can be restored with the addition of new microbes in the gut that would mimic healthy gut composition. New therapeutic strategies are involved in altering gut microbe to mimic gut microbiota found in healthy humans to restore the resistance capacity of gut microbe towards the disease (Cerdó et al. 2019). Different microbiome-targeted

therapies such as prebiotic-resistant starches (fiber), probiotics, and fecal microbiota transplantation are in play to replenish the microbiota composition in aid to treat diseases (Zhou et al. 2020). The role of the prebiotic and its influence depends on the existing bacteria in the host. The combined approach of prebiotics and growing specific bacteria is known as synbiotics, may be promising in treating diseases (Li et al. 2019).

- *Prebiotics* (*Food Components*): Edible substance that helps to promote the growth of defined microbes to enhance the host health by restoring the stability of microbiota and decrease proinflammatory pathways.
- *Probiotics* (*live Microorganism*): Beneficial and active microbes are composed mainly of yeast, Lactobacillus, Actinomycetes, Bifidobacterium, Clostridium which assist in inhibiting harmful bacteria growth by colonizing in human reproductive systems and intestines through maintaining microecology of the host.
- *Fecal Microbiota Transplantation*: It is the transplantation of healthy human feces to the gastrointestinal tract (GIT) of the patient to develop healthy functional microbiota to treat extraintestinal and intestinal diseases.

In late 300 AD, in Eastern Jinn Dynasty, China Ge Hong's "Elbow Reserve Emergency" has a record in the treatment of patients with human waste for treating conditions like diarrhea, food poisoning, fever, and death (Zhou et al. 2020). Although prebiotic and probiotics have shown promising effects in several treatments, their molecular mechanism is still unknown (Vieira et al. 2013)**.** In an FMT study conducted inpatient with *C. difficile* infection, followed by transplantation, there is increased *Bacteroidetes* in the gut. The microbiota composition after FMT was like the donor and differences were observed in the metagenomic profile in recipients. Further studies are needed to identify a specific colony that can modulate the immunity of the host and prevent tumor development and also restore the balance between gut microbiota and host (Seekatz et al. 2014).

12.6 Microbiome in Mice and Humans

In gut microbiome study, researchers mostly use mice, as they share similar digestive tract. However, animal models like Zebrafish, drosophila, fruit fly, and the Hawaiian bobtail squid have also widely been used in the study of host–microbiota interactions. Mice genes share 99% of similarities with human genes and also have a close resemblance with microbiome phylum as in humans (Kostic et al. 2013a)**.**

In mice, the gut is different from the human due to low pH and oxygen tension in the intestine affecting the fidelity of human microbiota. The changes in the glycan profile of the mucus and around 4% of microbial gene sequences were found to be shared between humans and mice (Fessler et al. 2019a), leaving less scope of research using mice to mimic the human environment. Sequencing technologies

revealed that microbiota exhibit varied genetic sequences between hosts and within a host over time. This variation of microbiota can be like one nucleotide variant, short insertions and deletions, and more substantial structural variations like deletions, insertions, duplications, inversions, and gene copy-number variants (Garud and Pollard 2020). Microbiome composition in humans evolves in the first 3 years after birth and then stabilizes and tends to remain constant until being affected by external and internal factors. Among microbiota, the gut has most of it, with approximately 3×10^{13} bacterial cells count ten times to the number of human cells (Roy and Trinchieri 2017).

12.7 Role of the Microbiome in Healthy Individuals

Microbiota is potential enough in transforming a variety of metabolites like some proteins, impacting the immune response in protecting the host from cancer generation and progression (Prosperi 2020). Gut microbiota and its products have been observed to be influencing the anticancer effect by modulating the immune system of the host through the immunological cell death pathway (Chen et al. 2020). Eubiosis, a rich and diverse microbiota regulating micro-ecological balance within the host, helps to maintain immunity by activating TLR signaling pathway acting as an adjuvant enhancing the immune response (Li et al. 2019). The gut microbiome regulates the homeostasis of the host intestine by processing the dietary fiber ingredients consumed by the host into digestible byproducts and plays an important role in eliciting an immune response against invading microbes and resisting them (Shui et al. 2020). It is demonstrated that the microbiome has been involved in the maturation of immune cells like CD4+ T cells, CD8+ T cells, and dendritic cells (Zhou et al. 2020). SCFA, such as butyrate, is generated by the dietary fibers through microbial fermentation, the primary energy source for the colonocytes (Fulbright et al. 2017). Butyrate is sensed by the dendritic cells, T cells expressing G protein-coupled receptors, GPR41 or 43 (Zitvogel et al. 2018). Glucose obtained from glycolysis becomes the primary carbon source for the cancer cells; this is known as the "Warburg Effect." In a diet with high fiber, content butyrate is produced and due to its impaired metabolism, there is a high percentage of the butyrate making the cancer cells starve.

Also, butyrate promotes apoptosis, inhibits histone deacetylase, regulates immunogenic cell death (ICD), cellular proliferation through epigenetic modifications (Fulbright et al. 2017). *Bifidobacterium infantis* involve in the differentiation of immune cells Tregs and dendritic cells and promote Foxp3+ regulatory T cells. *Clostridium butyricum* maintains intestinal immune homeostasis by regulating pancreatic T cells (Chen et al. 2020). Table 12.1 shows the systemic effects of gut microbiota on the host: The following functions in the human body are affected due to the gut microbiome impacting homeostasis leading to clinical disorders (Roy and Trinchieri 2017).

A good understanding of the bacteria gut microbiome is established. More research and details about the action of the virus and fungi composition and their

Table 12.1 Systemic effects of gut microbiota on the host physiology

Physiological functions	Non-neoplastic pathology
• Cardiovascular and musculoskeletal.Functions • Metabolism. • Neurological and cognitive functions. • Hematopoiesis and myeloid cell functions. • Inflammation and immunity. • Aging.	• Insulin resistance. • Obesity. • Autoimmune. • Non-alcoholic steatohepatitis.

interaction and their effect on the host would give complete handling of the human microbiota and utilize them efficiently as anticancer agents (Saus et al. 2019).

12.8 Microbiota Effects on Immune System Development

Initial colonization of intestinal bacteria depends upon gut-associated with lymphoid tissues (GALT); similarly, *Bacillus subtilis* and *Bacteroides fragilis* gut microbes have shown to promote GALT development (Rhee et al. 2004). GALT is a component of mucosa-associated lymphoid and they are divided into three sections (Cebra 1999):

(a) Payer patches (containing B cell and T cell),
(b) Lamina propria (consisting of immunoglobulins, dendritic cells, mast cells),
(c) Intraepithelial leukocyte spaces (NK cells, T cells).

Gut microbiota is involved in the maintenance of the mucosal immune system, during myelopoiesis, and the function of dendritic cells, macrophages, and neutrophils (Gorjifard and Goldszmid 2016; Fessler et al. 2019b). The mucosal immune system undergoes significant changes once bacterial colonization establishes in the intestinal tract. The gut microbiome has been shown to play a significant role in promoting NK cell differentiation, dendritic cells (Wu and Wu 2012). *B. fragilis* and *Clostridia* shape the polarity of macrophages and are observed to be coordinated mutualistic relationships between macrophages and microbes (Mezouar et al. 2018). Moreover, microbe-derived luminal ATP molecule activates $CD70^{high}$ $CD11c^{low}$ cells, which promotes TH17 cell differentiation (Atarashi et al. 2008).

Multiple diseases and chronic disorders had common intestinal dysbiosis that may have contributed to the pathogenicity of these diseases. Symbiotic bacteria are essential for lymphoid tissue development. Germ-free mice have shown gut-associated lymphoid tissues (GALT), developmental issues, and impaired lymphoid follicles compared to a pathogen-free mouse (Kim et al. 2017).

12.9 Microbiome Role in Epithelial Barrier

The epithelial barriers contain goblet cells, Paneth cells, on damage to these cells microbes infiltrate into the blood, few acting as the procarcinogenic agents to spread carcinogenesis and inflammation (Rajagopala et al. 2017). The gut epithelium and its tight junctions act as a barrier for a wide variety of bacteria and internal gut milieu, "at density up to 10^{12} organisms/ml intestinal content" were observed from a unicellular layer of epithelium (Sonnenburg et al. 2004). The luminal surface of gut epithelium cells prevents the entry of large particles and bacteria, preventing excessive immunological response, which affects gut health. IgA, IgM antibodies regulate the entry of antigen penetration across the epithelium layer. During an immune response, bacteria generate short-chain fatty acids, and these enhance the production of IgA (Li et al. 2019). IgA is crucial to maintain homeostasis of gut microbiota; its deficiencies cause the growth of anaerobic organisms in the gut cells (Suzuki et al. 2004). Short-chain fatty acids like acetate inhibit the growth of other pathogens and viruses, SCFA serves as an energy source for gut microbes (Mezouar et al. 2018).

12.10 Microbiome as a Marker

Most of the research studies explain that a specific microbe colony seems to be either dominant or causal of cancer development and progression. Alteration in the microbiome colonization due to antibiotics, vaccines, host genetics leads to cancers (Shahanavaj et al. 2015). Microbiome, highly populated microorganisms reside within the proximity of epithelium, soon be a way for the personalized medicine development targeting the pathobionts for the cancer progression (Fulbright et al. 2017). The altered microbiome can be a useful marker for diagnosing neoplasm primarily colorectal cancer (CRC), gastric cancer, cervical cancers. *F. nucleatum* found to be highly associated with the CRC in tumoral tissue and feces of the patients in comparison to the control individuals. SCFA, like butyrate, fructose, linoleic acid, acts as a robust diagnostic marker for CRC with low levels found in patients in comparison to control individuals (Saus et al. 2019).

Research studies explain that *B. longum*, *B. adolescentis*, *Parabacteroides merdae, Collinsella aerofaciens* are more populated in the feces of responder patients of melanoma and non-responders have dominated with *Ruminococcus obeum* and *Roseburia intestinalis* colonization (Elkrief et al. 2019).

Higher bacteroidales and low *B. fragilis* composition masking the effect of anti-CTLA-4 in melanoma patients was observed. Butyrate-producing bacterium and Firmicutes like *Faecalibacterium* genus involved with producing a higher response rate with more prolonged progression-free survival (Li et al. 2019).

Pancreatic cancer has been the most prominent and fourth leading cause of death, has some difficulty in early detection due to a lack of specific biomarkers. Recent research studies have been promising to overcome this situation in pancreatic cancer. *Porphyromonas gingivalis*, an oral bacterium is found to be increased in pancreatic

cancer. Patients tend to have antibodies against the bacteria *P. gingivalis* ATTC 53978. Also, saliva bacterial biomarkers are specific for the detection of pancreatic cancer (Shahanavaj et al. 2015).

12.11 Microbiome Affecting Cancer

Ongoing cancer research is focused on the human microbiota due to promising results shown in their interaction. The unknown proliferation of the cells is due to external and internal factors of the host affecting the development and progression of cancer. These factors are influenced by the microbiome activities within the host, indirectly affecting cancer. Microbiome in the host affects the remodeling of the tissue-like angiogenesis, a part of the tissue remodeling where adequate blood flow is developed, which is prior necessary for a tumor to get initiated. More investigation is required to understand the mechanism involved between microbiome and angiogenesis interaction (Fulbright et al. 2017). Therefore, the microbiota is observed to be important for the development of the vasculature in the intestines of the host.

Coley, in the nineteenth century, cures malignancies in humans using live cultures. There were few initial failures in the treatment but resulted in a mixture known as Coley's toxin composed of attenuated *Streptococcal* and *Serratia marcescens*. The success rate is 80% with 5 years survival rate treated around 1000 sarcoma patients in the period where the knowledge on cancer is still in its infancy. The mechanism behind the cure was toxins secreted by the composed mixture-induced immune response to fight against the malignant cells.

In 1863, Virchow explained the interrelation between inflammation and cancer onset, based on the studies detailed that carcinogenesis is initiated at the site of chronic inflammation. This concludes the direct microbiome effects on host cell physiology and changes in the equilibrium of the tissues. Modifications in the microbiome may result in undefined local and systemic inflammation and conditions within the host (Shahanavaj et al. 2015).

When cells stop to divide a condition known as cellular senescence, cells in the senescence state secrete growth factors, enable tumor growth, and the intestinal bacteria to induce malignancy. *E. coli* regulates senescence-associated phenotype (SASP) by secreting growth factors inducing tumor development and epithelial proliferation. Therefore, this bystander proliferation and microbial induced cellular senescence mechanisms caused due to microbial and host interactions develop malignancies (Fulbright et al. 2017). Some bacteria within the microbiome can induce chronic inflammation with or without an increase in the ROS, indicating their carcinogenic potential in the host. When the epithelial barriers are damaged by alterations, bacteria that get in direct contact with the host cell secrete toxins, leading to host DNA damage. Bacterial genotoxins like cytolethal distending toxin (CDT) and colibactin cause direct dsDNA damage and instability of the host genome, including phosphorylation of histone proteins and activation ataxia-telangiectasia mutated (ATM)–CHK2 signaling pathway. These genetic changes lead to cell swelling and cell cycle arrest at G2/M phase. Other toxins like *B. fragilis* toxin

and cytotoxic necrotizing factors affect the cellular responses and thus indirectly play a role in tumorigenesis (Schwabe and Jobin 2013).

Studies explain there is an increase in the interferon a/b signals in lung stromal cells, which aid in resist Influenza virus infection due to the gut microbiome. Researchers observed FMT enhances the immune system by altering the tumor microbiota. These promising observations allow defining cancer treatment by modifying the tumor immune micro-environment using the gut microbiota (Shui et al. 2020).

The gut microbiome has a significant impact on treating cancer and related toxicities in cancer-related therapies (Helmink et al. 2019). This explains that the gut microbiome has potential in overall cancer therapy. Gut microbiome alters the gut-associated lymphoid tissue and mucosa immune function through the interaction with PAMPs and antigen-presenting cells and TLRs, triggering an innate response in the host. These immune activities result in accelerated antitumor immune function with the low number of myeloid-derived suppressor cells (MDSCs) and high levels of tumor infiltration lymphocytes (TILs) (Helmink et al. 2019). Scientists revealed that patients have a higher diversity of the bacteria in their gut, who responded to the anti-PD-1 ICIs therapy compared to the non-responders. The diversity of the microbiota mainly includes an abundance of *Ruminococcus, Faecalibacterium, Clostridiales* (Gopalakrishnan et al. 2018). Further studies on the microbiota diversity generate more customized and increase the efficiency of cancer immunotherapy. Immunotherapy as a cancer treatment is an efficient way of utilizing the patient immune system to generate an antitumor effect with less adverse effects. Different approaches like sensitizing tumor cells as non-self to the immune system, immune checkpoint inhibitors (ICIs), a novel therapeutic agent with promising clinical results in malignancies. Monoclonal antibodies blocking PD-1/ PD-L-1, CTLA-4 blockade sensitize cancer cells to the patient immune system. Recent research studies explain that the gut microbiome affects the therapeutic efficacy of ICIs against cancer (Li et al. 2019). *B. fragilis* colonized in the mouse gut flora increased TH1 responses in the lymph nodes near to the tumor to enhance the efficacy of the CTLA-4 immune checkpoint inhibitor blockade (Elkrief et al. 2019).

The microbiome has proven to be a double-sided sword in cancer studies; wild type mice can combat carcinogenesis compared to germ-free mice, on the other end it can promote carcinogenesis by inducing inflammation to intestinal cells (Li et al. 2019) when there are alterations in the microbiome due to environmental or intrinsic factors affecting microbial structure (Zechner 2017). The chronic inflammation caused due to microbial dysbiosis has been known to promote cancer in the site of inflammation and also enhance the accumulation of *E. Coli.*

H. pylori is carcinogenic bacteria interacting with cell growth signaling pathways. Certain bacteria and viruses are known to cause fatal disease or chronic inflammation, as primary and secondary effects would be carcinogenic nature (Li et al. 2019). *H. pylori* have cytotoxin associated gene A (CagA) which produce virulence protein VacA, ureas, NapA2; the Vac A modulates β-catenin, resulting in inflammation and carcinogenesis (Rajagopala et al. 2017).

Fusobacterium nucleatum, an enterotoxigenic bacteria, when fed to ApcMin/+ mice, showed characteristics like human colorectal cancer with an abundance of the same bacteria in the tissues; however, few other mouse models did not exhibit any tumorigenesis (Kostic et al. 2013b). Other studies showed *F. nucleatum* virulence protein FadA activates the β-catenin pathway; alteration with NF-kB leads to inflammation and promotes a favorable tumor environment. Moreover, other virulence proteins like RadD induce the formation of biofilm from different bacteria, FaP2 binds to Gal-GalNAc, which promotes colonization of *F. nucleatum;* besides, it inhibits NK cells (Rajagopala et al. 2017). These studies suggest more details are required in signaling pathways between bacterial cells and host immune cells.

Certain bacterial species induce proinflammatory toxins, alteration in signaling pathways, also the production of genotoxic substances (Helmink et al. 2019). Some microbes are known to cause cancer other than inducing inflammation. Microbes produce toxic substances and some microbes themselves, when mixed with blood, get carried to distant locations in the body and can cause cancer (Rajagopala et al. 2017). Human papillomavirus, hepatitis B and C viruses, human cell leukemia virus, Epstein–Barr virus (EBV), Kaposi sarcoma-associated virus (KSHV) human, T lymphotropic virus one and all known to cause cancer in humans. EBV is associated with gastric cancer (Rajagopala et al. 2017). Virus composition in the human virome has been unexplored. Fungi and protozoa research studies are to be focused on knowing different microbiome genome interaction with host (Elinav et al. 2019).

12.12 Microbiome in Cancer Immunotherapy

12.12.1 CD47 Blockade with *Bifidobacteria*

The effect of immunotherapy in patients is influenced by the host gut's ability to resist invading pathogens and response to treatment. In the malignant mouse model, scientists found that anaerobic bacteria travel to tumor sites and boost effectiveness against immunotherapy. In tumor-bearing mice, the absence of gut bacteria did not respond to anti-CD47 antibiotics (Shi et al. 2020). Bifidobacteria present in the human gut travels and accumulates at the tumor site and blocks CD47 to increase the response against immunotherapy via stimulators of interferon genes (STING). In a similar study, mice with inactive STING pathways showed no benefit from bacteria-immunotherapy combined approach. STING is a transmembrane protein present on macrophages, T cells, dendritic cells. STING stimulates innate immune genes with respect to invading viruses, bacteria into the host. STING is activated by certain cyclic dinucleotides (CDNs) produced by certain bacteria, followed by subsequent reaction process type I interferons (IFNs) are secreted outside the cytoplasm of the cell (Barber 2015). Type I interferons are antiviral cytokines and regulate adaptive immune systems (Haller et al. 2006).

CD47 (cluster of domains) is a transmembrane protein; it is present in different cell types (Zhang et al. 2019) (Zhang et al. 2020). CD47 is an immunoglobulin

known as integrin associated protein (IAP). It is overexpressed in cancerous cells to avoid immune responses by acting as self-cells. High levels of CD47 in cancerous cells mask immunotherapy and its prognosis. One of its ligand, known as signal regulatory protein α (SIRPα) is a transmembrane protein present on myeloid cells such as monocytes, macrophages, granulocytes, and myeloid dendritic cells. Formation of CD47 and SIRPα signaling complex inhibits the build-up of myosin IIA in phagocytic synapses, which acts as a "do not eat me" signal. Blocking this CD47 has potential in cancer treatment and has been used in various immunotherapies. Monoclonal antibodies against this complex have proven to be an effective therapy for solid tumor and hematologic malignancies (Folkes et al. 2018).

12.12.2 PD-L1 Blockade Assisted with *Bifidobacterium*

Bifidobacterium (gram +ve) found in the healthy gastrointestinal tract, which helps in digestion and produces vitamin K and B, codes for carbohydrate digestive enzymes, also used in probiotics (O'Callaghan and van Sinderen 2016). This organism has shown antitumor activity when subjected to mice with melanoma. *Bifidobacterium*, along with programmed cell death protein1 ligand (PD-L1), abrogated cancer with enhanced CD8 + T cells (Sivan et al., 2015).

12.12.3 CTLA-4 Blockade Assisted with *Bacteroidales*

CTLA-4 binding achieved with monoclonal antibody studied in patients with III/IV stage melanoma faced effects on gastrointestinal immunity (Berman et al. 2010). In fecal microbial transplantation (FMT) study conducted in mice proved the microbial influence of blocking of CTLA-4. *B. fragilis*, *B. thetaiotaomicron,* and *Burkholderiales* played a significant role in antitumor activity with the help of interleukin 12(IL-12) dependent T cells (Vétizou et al. 2015). Contradicting the above statement, *Bacteroides fragilis* is an enterotoxigenic bacteria; its abundance was co-related to colorectal cancer by a study conducted in 150 humans (Purcell et al. 2017).

12.12.4 Short-Chain Fatty Acids in Treatment for Cancer

The most prominently studied SCFAs are acetate, butyrate, and propionate compared to valerate and caproate. The abundant SCFA like acetate, butyrate, and propionate is produced in the ratio of 60:20:20 (Chambers et al. 2018). Acetate, butyrate, propionate, valerate, and caproate were used in a study to understand the effects of SCFA in apoptosis and cancer. This study concluded that the butyrate was more potent to compare to propionate and valerate to induce cell growth arrest and differentiation in colon cancer cell lines. A related study showed that this ability of SCFA depends on histone hyperacetylation effects, alteration in cell cycle regulators

p21 and CB1. Butyrate enhanced histone acetylation compared to other SCFA and increased the rate of programmed cell death. The exact mechanisms of action is not well known; it has been proposed that butyrate modifies chromatin structure by inhibiting histone deacetylase resulting in hyperacetylation of core proteins. During histone acetylation, the DNA becomes loosely packed to histone protein and is available for transcription of specific genes like cell regulators, chemokines (Hinnebusch et al. 2002).

The chemokines expressed by the epithelial cells like IL-8 and MCP-1 are found to attract neutrophils and monocytes (Fusunyan et al. 1999). Butyrate, with the help of p21 protein downregulated Cyclin B1(CB1), is found in a study conducted on HT-29 cells. CB1 is a crucial component for health development; its increased levels are found in colon cancer (Hinnebusch et al. 2002). It can control p53 mitotic cell division through regulating CB1 levels and preventing neoplastic transformation (Innocente et al. 1999). Cyclin B1 plays a critical role in cell cycle progression from G2 to M phase, with the involvement of NF-κB. Studies are explaining that CB1 has induced tumor malignancy in esophageal cancer (Zhan et al. 2012).

It is studied that chronic intestinal inflammation causes cancer in the intestine; also, it leads to pattern alteration in epithelial differentiation leading to an undifferentiated state. Interleukin-8, a proinflammatory cytokine induces differentiation in epithelial cells, butyrate has shown inhibition of IL-8 also can induce differentiation of cells in vivo (Huang et al. 1997). SCFA are known to directly activate G-coupled protein receptors like GPR43, GPR109A, and GPR41, which activate anti-inflammatory cascades (Venegas et al. 2019) (Lazar et al. 2018). The detailed illustration is in Fig. 12.2.

12.13 Future Perspectives

We are in the era of the microbiome, which has more positive preclinical and clinical research in treating cancer. Furthermore, few challenges are upfront to know how to regulate gut microbiota and the interaction of other genomes in the microbiome to improve the efficacy of cancer immunotherapy. Targeting cancer immunotherapy through the microbiome can be more successful and improve immune surveillance when the favorable components of the microbiome are completely defined. FMT in anticancer therapy acts as a promising way to treat cancers if the donor composition is well known. The favorable bacteria composed of *Akkermansia muciniphila, Bifidobacteria* spp., *E. hirae*, and *Bacteroides* spp. are found to impact malignant cells effectively. Finalizing the set of microbes for treating cancer can be done by filling the research gap, knowing the interaction of other microbial genomes with hosts like viruses, archaea, protists, and fungi would be more promising in treating cancers and building personalized medicine.

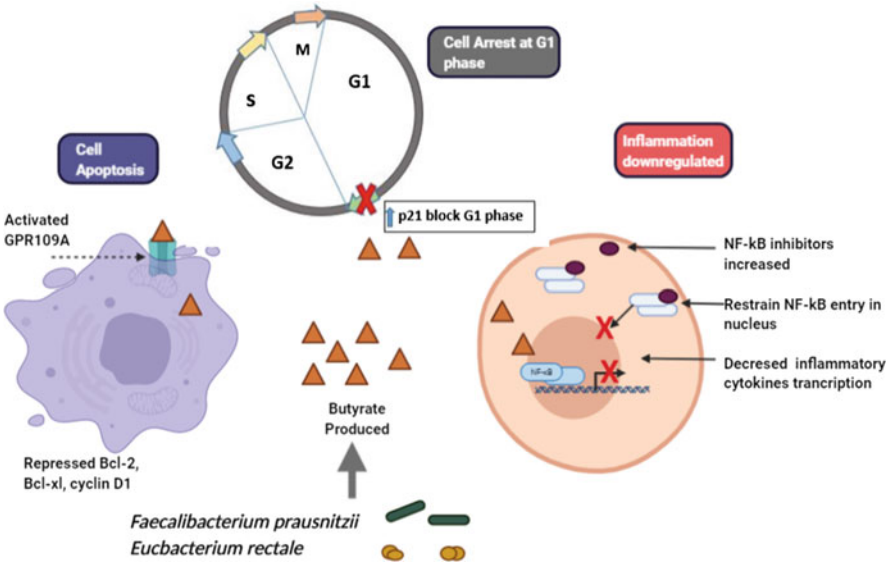

Fig. 12.2 SCFA production and its impact in different ways on the immune system of the host. When the host consumes a high fiber diet, interbacterial fermentation by *Faecalibacterium prausnitzii, Eubacterium rectale* produces high SCFA like butyrate and activates some immune proteins to kill cancer cells by apoptosis, ell cycle arrest at G1 phase, by downregulation of inflammation (Canani et al. 2011) (Segain et al. 2000)

12.14 Conclusion

Microbiomes within the body can be a good source in treating cancer growth without any adverse effect on the host body. The host–microbiome plays a crucial role in maintaining homeostasis of the immune system and its study can be an efficient and economical way of developing a treatment for cancer and other microbial diseases. The interaction between the host immunity, microbiome, and cancer progression is explained to an extent, but more studies are to be performed. Microbiomes have been affected by many factors, these alterations modifying the favorable microbiome to unhealthy ones. Different microbes act as a marker specific to cancer and have been used as an early diagnostic route to detect them. Immunotherapy is an existing way of treating cancers, microbiome playing a considerable role in the effect of immunotherapy enhances the antitumor effects in the patients. To conclude, we are in a state of a holistic vision of using the microbiome as a strategy in cancer immunotherapy. In the coming years, more studies on other genomes of the microbiomes and their interaction would strengthen the knowledge on the microbiome and make it a promising way to treat cancer.

Acknowledgments The corresponding author Dr. Pola Sudhakar would like to express his deepest thanks to authorities of Andhra University, Visakhapatnam, India for providing necessary facilities to carry out the research work and for extending constant support.

Conflict of Interest The authors declare that there is no potential conflict of interest.

References

Allaband C, McDonald D, Vázquez-Baeza Y, Minich JJ, Tripathi A, Brenner DA, Loomba R, Smarr L, Sandborn WJ, Schnabl B, Dorrestein P, Zarrinpar A, Knight R (2019) Microbiome 101: studying, analyzing, and interpreting gut microbiome data for clinicians. Clinical Gastroenterology and Hepatology 17(2):218–230. https://doi.org/10.1016/j.cgh.2018.09.017

Atarashi K, Nishimura J, Shima T, Umesaki Y, Yamamoto M, Onoue M, Yagita H, Ishii N, Evans R, Honda K, Takeda K (2008) ATP drives lamina propria TH17 cell differentiation. Nature 455:808–812. https://doi.org/10.1038/nature07240

Barber GN (2015) STING: infection, inflammation and cancer. Nature Reviews Immunology 15 (12):760–770. https://doi.org/10.1038/nri3921

Berman D, Parker SM, Siegel J, Chasalow SD, Weber J, Galbraith S, Targan SR, Wang HL (2010) Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma. Cancer Immun 10:11

Canani RB, Di Costanzo M, Leone L, Pedata M, Meli R, Calignano A (2011) Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World J Gastroenterol 17 (12):1519–1528. https://doi.org/10.3748/wjg.v17.i12.1519

Cebra JJ (1999) Influences of microbiota on intestinal immune system development. Am J Clin Nutr 69:1046–1051. https://doi.org/10.1093/ajcn/69.5.1046s

Cerdó T, García-Santos JA, Bermúdez MG, Campoy C (2019) The role of probiotics and prebiotics in the prevention and treatment of obesity. Nutrients 11(3):635. https://doi.org/10.3390/nu11030635

Chambers ES, Preston T, Frost G, Morrison DJ (2018) Role of gut microbiota-generated short-chain fatty acids in metabolic and cardiovascular health. Current Nutrition Reports 7(4):198–206. https://doi.org/10.1007/s13668-018-0248-8

Chen W, Wang S, Wu Y, Shen X, Guo Z, Li Q, Xing D (2020) Immunogenic cell death: a link between gut microbiota and anticancer effects. Microb Pathog 141:103983. https://doi.org/10.1016/j.micpath.2020.103983

Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, Cox LM, Amir A, Gonzalez A, Bokulich NA, Song SJ, Hoashi M, Rivera-Vinas JI, Mendez K, Knight R, Clemente JC (2016) Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. Nat Med 22 (3):250–253

Elinav E, Garrett WS, Trinchieri G, Wargo J (2019) The cancer microbiome. Nat Rev Cancer 19 (7):371–376. https://doi.org/10.1038/s41568-019-0155-3

Elkrief A, Derosa L, Zitvogel L, Kroemer G, Routy B (2019) The intimate relationship between gut microbiota and cancer immunotherapy. Gut Microbes 10(3):424–428. https://doi.org/10.1080/19490976.2018.1527167

Fessler J, Matson V, Gajewski TF (2019a) Exploring the emerging role of the microbiome in cancer immunotherapy. Journal for Immuno Therapy of Cancer 7(1):1–15. https://doi.org/10.1186/s40425-019-0574-4

Fessler J, Matson V, Gajewski TF (2019b) Exploring the emerging role of the microbiome in cancer immunotherapy. J Immunother Cancer 7(1):1–15. https://doi.org/10.1186/s40425-019-0574-4

Folkes AS, Feng M, Zain JM, Abdulla F, Rosen ST, Querfeld C (2018) Targeting CD47 as a cancer therapeutic strategy: the cutaneous T-cell lymphoma experience. Current Opinion in Oncology 30:332. https://doi.org/10.1097/CCO.0000000000000468

Fulbright LE, Ellermann M, Arthur JC (2017) The microbiome and the hallmarks of cancer. PLoS Pathog 13:1–6. https://doi.org/10.1371/journal.ppat.1006480

Fusunyan RD, Quinn JJ, Fujimoto M, MacDermott RP, Sanderson IR (1999) Butyrate switches the pattern of chemokine secretion by intestinal epithelial cells through histone acetylation. Mol Med 5(9):631–640. https://doi.org/10.1007/bf03402075

Garud NR, Pollard KS (2020) Population genetics in the human microbiome. Trends Genet 36 (1):53–67. https://doi.org/10.1016/j.tig.2019.10.010

Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA (2018) The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. Cancer Cell 33(4):570–580. https://doi.org/10.1016/j.ccell.2018.03.015

Gorjifard S, Goldszmid RS (2016) Microbiota—myeloid cell crosstalk beyond the gut. J Leukoc Biol 100(5):865–879. https://doi.org/10.1189/jlb.3ri0516-222r

Haller O, Kochs G, Weber F (2006) The interferon response circuit: induction and suppression by pathogenic viruses. Virology 344(1):119–130. https://doi.org/10.1016/j.virol.2005.09.024

Helmink BA, Khan MAW, Hermann A, Gopalakrishnan V, Wargo JA (2019) The microbiome, cancer, and cancer therapy. Nat Med 25:377. https://doi.org/10.1038/s41591-019-0377-7

Hinnebusch BF, Meng S, Wu JT, Archer SY, Hodin RA (2002) The effects of short-chain fatty acids on human colon cancer cell phenotype are associated with histone hyperacetylation. J Nutr 132(5):1012–1017. https://doi.org/10.1093/jn/132.5.1012

Huang N, Katz JP, Martin DR, Wu GD (1997) Inhibition of IL-8 gene expression in Caco-2 cells by compounds which induce histone hyperacetylation. Cytokine 9:27. https://doi.org/10.1006/cyto.1996.0132

Innocente SA, Abrahamson JLA, Cogswell JP, Lee JM (1999) p53 regulates a G2 checkpoint through cyclin B1. Proc Natl Acad Sci USA 96:2147. https://doi.org/10.1073/pnas.96.5.2147

Kho ZY, Lal SK (2018) The human gut microbiome—a potential controller of wellness and disease. Frontiers in Microbiology 9:1835. https://doi.org/10.3389/fmicb.2018.01835

Kim D, Zeng MY, Núñez G (2017) The interplay between host immune cells and gut microbiota in chronic inflammatory diseases. Experimental and Molecular Medicine 30:492–506. https://doi.org/10.1038/emm.2017.24

Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, El-Omar EM, Brenner D, Fuchs CS, Meyerson M, Garrett WS (2013a) Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host and Microbe 14(2):207–215. https://doi.org/10.1016/j.chom.2013.07.007

Kostic AD, Howitt MR, Garrett WS (2013b) Exploring host-microbiota interactions in animal models and humans. Genes Dev 27(7):701–718. https://doi.org/10.1101/gad.212522.112

Lazar V, Ditu LM, Pircalabioru GG, Gheorghe I, Curutiu C, Holban AM, Picu A, Petcu L, Chifiriuc MC (2018) Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer. Frontiers in Immunology 9:1830. https://doi.org/10.3389/fimmu.2018.01830

Li W, Deng Y, Chu Q, Zhang P (2019) Gut microbiome and cancer immunotherapy. Cancer Lett 447:41–47. https://doi.org/10.1016/j.canlet.2019.01.015

Lv J, Guo L, Liu JJ, Zhao HP, Zhang J, Wang JH (2019) Alteration of the esophageal microbiota in Barrett's esophagus and esophageal adenocarcinoma. World J Gastroenterol 25(18):2149–2161. https://doi.org/10.3748/wjg.v25.i18.2149

Methé BA, Nelson KE, Pop M, Creasy HH, Giglio MG, Huttenhower C, Gevers D, Petrosino JF, Abubucker S, Badger JH, Chinwalla AT, Earl AM, Fitzgerald MG, Fulton RS, Hallsworth-Pepin K, Lobos EA, Madupu R, Magrini V, Martin JC, White O (2012) A framework for human microbiome research. Nature 486(7402):215–221. https://doi.org/10.1038/nature11209

Mezouar S, Chantran Y, Michel J, Fabre A, Dubus JC, Leone M, Sereme Y, Mège JL, Ranque S, Desnues B, Chanez P, Vitte J (2018) Microbiome and the immune system: from a healthy steady-state to allergy associated disruption. Human Microbiome Journal 10:11–20. https://doi.org/10.1016/j.humic.2018.10.001

O'Callaghan A, van Sinderen D (2016) Bifidobacteria and their role as members of the human gut microbiota. Frontiers in Microbiology 2015:01030. https://doi.org/10.3389/fmicb.2016.00925

Prosperi D (2020) Preface: Frontiers in cancer immunotherapy: understanding the role of gut microbiota. Curr Pharm Biotechnol 21(1):2–2. https://doi.org/10.2174/1389201021011912091633 06

Purcell RV, Pearson J, Aitchison A, Dixon L, Frizelle FA, Keenan JI (2017) Colonization with enterotoxigenic Bacteroides fragilis is associated with early-stage colorectal neoplasia. PLoS One 12(2):e0171602. https://doi.org/10.1371/journal.pone.0171602

Rajagopala SV, Vashee S, Oldfield LM, Suzuki Y, Venter JC, Telenti A, Nelson KE (2017) The human microbiome and cancer. Cancer Prev Res 10(4):226–234. https://doi.org/10.1158/1940-6207.CAPR-16-0249

Rhee K-J, Sethupathi P, Driks A, Lanning DK, Knight KL (2004) Role of commensal bacteria in development of gut-associated lymphoid tissues and preimmune antibody repertoire. J Immunol 172(2):1118–1124. https://doi.org/10.4049/jimmunol.172.2.1118

Roy S, Trinchieri G (2017) Microbiota: a key orchestrator of cancer therapy. Nat Rev Cancer 17 (5):271–285. https://doi.org/10.1038/nrc.2017.13

Saus E, Iraola-Guzmán S, Willis JR, Brunet-Vega A, Gabaldón T (2019) Microbiome and colorectal cancer: roles in carcinogenesis and clinical potential. Mol Asp Med 69:93–106. https://doi.org/10.1016/j.mam.2019.05.001

Schwabe RF, Jobin C (2013) The microbiome and cancer. Nat Rev Cancer 13(11):800–812. https://doi.org/10.1038/nrc3610

Seekatz AM, Aas J, Gessert CE, Rubin TA, Saman DM, Bakken JS, Young VB (2014) Recovery of the gut microbiome following fecal microbiota transplantation. MBio 5(3):e00893. https://doi.org/10.1128/mBio.00893-14

Segain JP, Raingeard de la Blétière D, Bourreille A, Leray V, Gervois N, Rosales C, Ferrier L, Bonnet C, Blottière HM, Galmiche JP (2000) Butyrate inhibits inflammatory responses through NFkappaB inhibition: implications for Crohn's disease. Gut 47(3):397–403

Shahanavaj K, Gil-Bazo I, Castiglia M, Bronte G, Passiglia F, Carreca AP, Del Pozo JL, Russo A, Peeters M, Rolfo C (2015) Cancer and the microbiome: potential applications as new tumor biomarker. Expert Review of Anticancer Therapy 15(3):317–330. https://doi.org/10.1586/14737140.2015.992785

Shi Y, Zheng W, Yang K, Harris KG, Ni K, Xue L, Lin W, Chang EB, Weichselbaum RR, Fu YX (2020) Intratumoral accumulation of gut microbiota facilitates CD47-based immunotherapy via STING signaling. J Exp Med 217(5):e20192282. https://doi.org/10.1084/jem.201922

Shui L, Yang X, Li J, Yi C, Sun Q, Zhu H (2020) Gut microbiome as a potential factor for modulating resistance to cancer immunotherapy. Front Immunol 10:1–16. https://doi.org/10.3389/fimmu.2019.02989

Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, Benyamin FW, Lei YM, Jabri B, Alegre ML, Chang EB, Gajewski TF (2015) Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 350 (6264):1084–1089. https://doi.org/10.1126/science.aac4255

Sonnenburg JL, Angenent LT, Gordon JI (2004) Getting a grip on things: how do communities of bacterial symbionts become established in our intestine? Nature Immunology 5:569–573. https://doi.org/10.1038/ni1079

Suzuki K, Meek B, Doi Y, Muramatsu M, Chiba T, Honjo T, Fagarasan S (2004) Aberrant expansion of segmented filamentous bacteria in IgA-deficient gut. Proc Natl Acad Sci USA 101(7):1981–1986. https://doi.org/10.1073/pnas.0307317101

Temraz S, Nassar F, Nasr R, Charafeddine M, Mukherji D, Shamseddine A (2019) Gut microbiome: a promising biomarker for immunotherapy in colorectal cancer. International Journal of Molecular Sciences 20:4155. https://doi.org/10.3390/ijms20174155

Ursell LK, Metcalf JL, Parfrey LW, Knight R (2012) Defining the human microbiome. Nutr Rev 70:38–44. https://doi.org/10.1111/j.1753-4887.2012.00493.x

Venegas DP, De La Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, Harmsen HJM, Faber KN, Hermoso MA (2019) Short chain fatty acids (SCFAs) mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Frontiers in Immunology 10:277. https://doi.org/10.3389/fimmu.2019.00277

Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, Rusakiewicz S, Routy B, Roberti MP, Duong CPM, Poirier-Colame V, Roux A, Becharef S, Formenti S, Golden E, Cording S, Eberl G, Schlitzer A, Ginhoux F et al (2015) Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 350(6264):1079–1084. https://doi.org/10.1126/science.aad1329

Vieira AT, Teixeira MM, Martins FS (2013) The role of probiotics and prebiotics in inducing gut immunity. Frontiers in Immunology 4:445. https://doi.org/10.3389/fimmu.2013.00445

Wu HJ, Wu E (2012) The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes 3(1):4–14. https://doi.org/10.4161/gmic.19320

Zechner EL (2017) Inflammatory disease caused by intestinal pathobionts. Current Opinion in Microbiology 35:64–69. https://doi.org/10.1016/j.mib.2017.01.011

Zhan QM, Wang LH, Song YM, Ou YQ, Jiang J, Fan J, Wang JB, Shen J (2012) Esophageal carcinoma. In: Recent Advances in Cancer Research and Therapy. Elsevier, Burlington. https://doi.org/10.1016/B978-0-12-397833-2.00018-2

Zhang W, Huang Q, Xiao W, Zhao Y, Pi J, Xu H, Zhao H, Xu J, Evans CE, Jin H (2020) Advances in anti-tumor treatments targeting the CD47/SIRPα Axis. Front Immunol 11:1–15. https://doi.org/10.3389/fimmu.2020.00018

Zhang X, Wang Y, Fan J, Chen W, Luan J, Mei X, Wang S, Li Y, Ye L, Li S, Tian W, Yin K, Ju D (2019) Blocking CD47 efficiently potentiated therapeutic effects of anti-angiogenic therapy in non-small cell lung cancer. J Immunother Cancer 7(1):346. https://doi.org/10.1186/s40425-019-0812-9

Zhou A, Tang L, Zeng S, Lei Y, Yang S, Tang B (2020) Gut microbiota: a new piece in understanding hepatocarcinogenesis. Cancer Lett 474:15–22. https://doi.org/10.1016/j.canlet.2020.01.002

Zitvogel L, Ma Y, Raoult D, Kroemer G, Gajewski TF (2018) The microbiome in cancer immunotherapy: diagnostic tools and therapeutic strategies. Science 359(6382):1366–1370. https://doi.org/10.1126/science.aar6918