# Emerging Role of Gut Microbiome in Cancer Immunotherapy

18

Meghali Bharti, Sonakshi Modeel, Sheetal Yadav, Pankaj Yadav, Sneha Siwach, Padma Dolkar, Shekhar Nagar, Tarana Negi, and Ram Krishan Negi

**Abstract**

Current scientific advances have considerably added to our understanding of the complex association between the microbiome and cancer. Host and microbiota have co-evolved into a "super-organism," and several physiological processes and multifactorial disease conditions are influenced by host–microbiome interactions. In the past, microbial communities have been suggested to influence the development, progression, metastasis formation, and treatment response of multiple cancer types. However, a better molecular understanding of cancer-modulating interactions and influences on cancer treatment is considered of major scientific relevance and clinical importance. Here, we discuss the scientific evidence on the role of gut microbiota in cancer progression and its treatment and highlight the latest knowledge leveraged to target specific microbes contributing to tumorigenesis.

**Keywords**

Microbiome · Carcinogenesis · Therapy · Immunity

M. Bharti · S. Modeel · S. Yadav · P. Yadav · S. Siwach · P. Dolkar · R. K. Negi (✉)
Fish Molecular Biology Laboratory, Department of Zoology, University of Delhi, Delhi, India

S. Nagar
Fish Molecular Biology Laboratory, Department of Zoology, University of Delhi, Delhi, India

Present Address: Deshbandhu college, University of Delhi, Delhi, India

T. Negi
Department of Zoology, Government College, Dujana, India



R. Sobti et al. (eds.), *Role of Microbes in Sustainable Development*,
https://doi.org/10.1007/978-981-99-3126-2_18

## 18.1 Introduction

Microbes represent wide ecological adaptations dominating all four spheres of the earth and in that way captivate microbiologists to explore their niches. A narrative of the terminology has been proposed explaining that microbial taxa linked to a host organism or a dominant environment refer to "microbiota," whereas the "microbiome" is the exclusive assemblage of the microbes and their associated genes (Ursell et al. 2012). Next-generation sequencing (NGS) techniques have garnered ample attention for providing a comprehensive view of human microbiome. The human microbiome is a multi-kingdom repertoire of bacteria, archaea, fungi, protists, and viruses residing in and on the human body (Ursell et al. 2012). Microbiome performs vital functions such as regulating barrier, maintaining homeostasis, preventing pathogenic infection, and regulating metabolism and vitamin synthesis (Li et al. 2019). Oral, gut, and skin microbiomes comprise greatly enriched and diverse microbial consortia, whereas lungs, bladder, prostate, liver, pancreas, and vagina harbor low diverse microbial populations (Cho and Blaser 2012). The host and its microbiome exist in symbiosis as a super-organism by offering a nutrient-rich microenvironment (Schwabe and Jobin 2013). Despite the presence of trillions of beneficial microbes inhabiting human body, dysbiosis can still occur that might lead to the development of cancers and inflammatory diseases. Microbial diversity and abundance differ in different organs; thus, many diseases, including cancer, occur in specific locations within an organ. Chances of cancer are high in those locations where microbial densities are high (Human Microbiome Project Consortium 2012; Cullin et al. 2021).

Investigation of evidence of microbial influence on biology of cancer is in its infancy, and a better comprehensive view of cancer-modeling interfaces and its influence on cancer treatment are reflected as of great scientific relevance. Composition and functional repertoire of microbial communities can be characterized and used for defining pathology and physiology of human cancers (Cullin et al. 2021). Human bodies are continuously exposed to variety of microbes and their byproducts including some tumor-promoting metabolites such as high levels of polyamines, sulfides, and *N*-nitroso compounds (Louis et al. 2014). These metabolites while circulating in the body may lead to cancer progression at locations distinct from the specific microbial residence (Rajagopala et al. 2017). Microorganisms can also migrate to different locations and get associated with the development of tumors. However, the microbes impact the process of carcinogenesis by inflammation and immune system-independent mechanisms and the most decipherable link is via the immune system as the microbes themselves play a significant role in activating and regulation of host immunity (Rajagopala et al. 2017). Interaction of immune system and microorganisms can occur at (1) mucosal layers (via microbial metabolites) or (2) locally at lymphoid organs. Remote/local microbial signals may impact both innate and adaptive immune responses, leading to systemic immunity modulation and anti-tumor innate immune responses (Cullin et al. 2021). Microorganisms can modulate metabolism, inflammation, carcinogenesis, and genotoxicity through multiple mechanisms, and targeting these mechanisms could envision cancer prevention

strategies. Genetic modification of microbiota producing/lacking particular enzymes could be utilized for expressing tumor-reducing phytochemicals or reducing tumor-promoting elements (Shwabe and Jobin 2013).

By means of proliferation, escaping cell growth suppression, activation of metastatic pathways, angiogenesis induction, and autophagy resistance cancer cells evade the immune system. All these processes have been explored in detail for decades, but role of microbiome in both cancer progression and treatment is still partly unknown. Microbiome data analysis may assist the advancement of novel cancer diagnostic strategies encompassing cancer detection (identification of microbial DNA/RNA in peripheral blood), surveying metastatic cancer progression, assessing prognosis, and applying artificial intelligence algorithms in foreseeing patient treatment responses. The understanding of the microbiome and cancer needs to be broadened with enhanced feasibility of cancer diagnosis based on microbial profile. Exploring various effects of the microbiome on carcinogenesis will provide new opportunities for diagnostic, preventive, and therapeutic strategies and would represent the next frontier of medical research.

## 18.2 Cancer Triggering Microbes and Their Cancer-Promoting Mechanisms

Hepatitis B (HBV), Epstein–Barr (EBV), hepatitis C (HCV), Kaposi sarcoma herpesvirus (KSV), human immunodeficiency virus-1 (HIV), human papillomaviruses (HPV), human T cell lymphotropic virus type 1 (HTLV), *Opisthorchis viverrini, Clonorchis sinensis, Schistosoma haematobium*, and *Helicobacter pylori* have been recognized as causes of distinct human cancer (IARC 2009). They participate in cancer progression through different mechanisms, such as B-cell differentiation, cell-cycle disruption, immune hyperactivation (HBV, EBV, HIV, and HCV), dysregulation of T cell (HTLV, EBV), and direct oncogenesis (HCV). Merkel cell polyomavirus (MCV) and Simian virus 40 (SV40) are involved in Merkel cell carcinoma (MCC) and mesothelioma, respectively (Pagano et al. 2004; Weitzman and Weitzman 2014).

In the case of *H. pylori*, CagA dissociates E-cadherin/b-catenin complex, leading to accumulation of b-catenin in both nucleoplasm and cytoplasm (Fig. 18.1). Further, this b-catenin forms complex with transcription factors (TCF/LEF) to activate target gene expression (Hamway et al. 2020). It binds to gastric epithelial cells by HopQ binding to CEACAM, whereby virulence factor CagA is directly injected into the epithelial cells via the T4SS. CagA activates Wnt/β-catenin pathways resulting in dysregulated cellular turnover and apoptosis (Cullin et al. 2021). On the other hand, *F. nucleatum* secretes Fap2 protein that interacts with TIGIT and hinders natural killer cell-facilitated immunosurveillance of cancer (Fig. 18.1). Another important adhesion, FadA, allows cellular internalization and induction of proinflammatory cascades mediated by NF-κB and IL-6. Fap2 interacts with D-galactose-β (1–3)-N-acetyl-D-galactosamine (Gal-GalNAc) carbohydrate moieties at the tumor surface to enhance cellular proliferation via Wnt/β-catenin pathway and increase

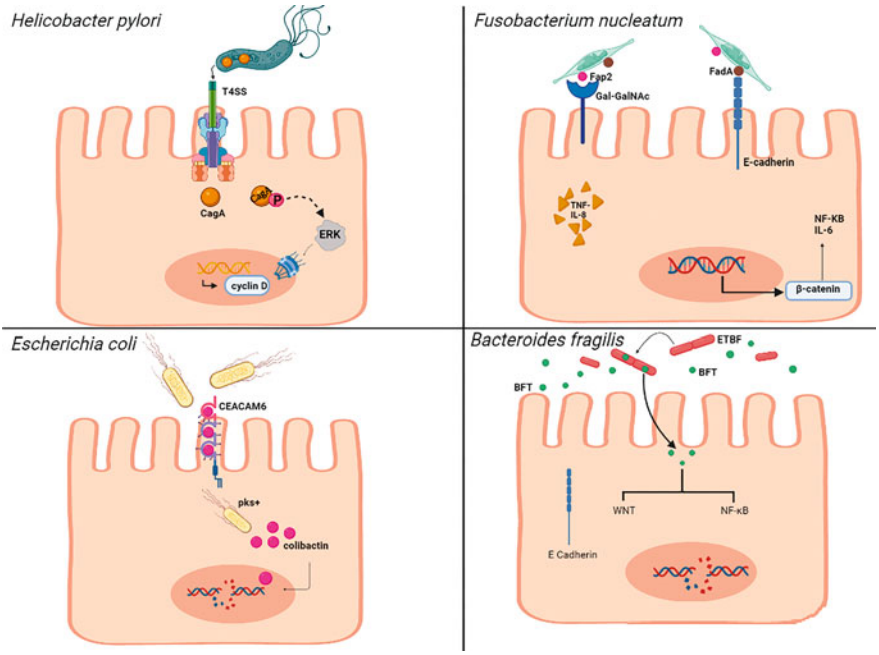


**Fig. 18.1** Impact of microbes and their cancer-triggering mechanisms

proinflammatory cytokine production, leading to cancer cell invasion and therapy resistance (Zhang et al. 2020; Cullin et al. 2021).

The intestinal dysbiosis favors growth of adherent-invasive *Escherichia coli* (AIEC) and activation of pks island during inflammation, which increases IL-6-inducing CEACAM6 expression, hence increasing invasiveness of AIEC (Cullin et al. 2021). Once internalized, it secretes genotoxin colibactin, which induces inter-strand crosslink and double-stranded breaks with pro-tumoral cellular transformation (Fig. 18.1). Likewise, the enterotoxigenic *Bacteroides fragilis* (ETBF) produce BFT that can disrupt the intestinal environment by causing inflammation and increased permeability. BFT targets intestinal cell tight junction and causes cleavage of E-cadherin, which causes increased intestinal permeability and induces chronic intestinal inflammation via NF_KB signaling, leading to colorectal tumorigenesis (Fig. 18.1) (Pleguezuelos-Manzano et al. 2020).

## 18.3 Mechanisms of Microbial Carcinogenesis

Mechanism of microbial carcinogenesis involves (a) inflammation: Bacterial translocation may increase due to change in microbiome and host defense system, which leads to inflammation mediated by microorganism-associated molecular patterns (MAMPs) that activate Toll-like receptors (TLRs) in various cells like macrophage,

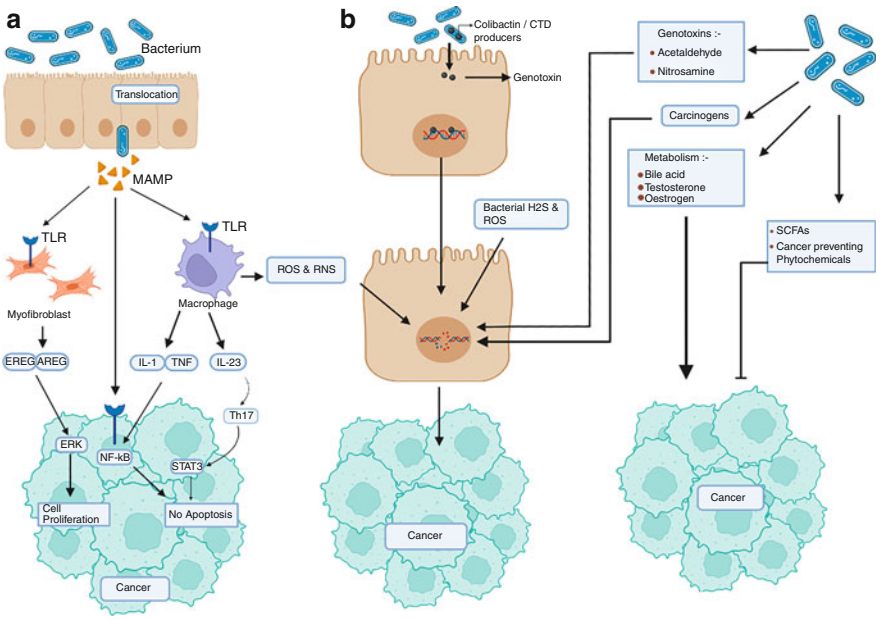


**Fig. 18.2** Mechanism of bacterial microbiome-mediated carcinogenesis

myofibroblasts, and tumor cells; (b) genotoxin effect: Bacterial genotoxins like colibactin and cytolethal distending toxin (CTD), which when delivered to host cell nucleus cause DNA damage in various organs (Cullin et al. 2021). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) released from inflammatory cells like macrophage and hydrogen sulfide ($H_2S$) from bacterial microbiota may also be genotoxic, thus triggering carcinogenesis; (c) metabolic effect: Genotoxins like acetaldehyde, dietary nitrosamine in metabolism of bile acids, and hormones like estrogen and testosterone may activate due to metabolic actions of microbiome. The microbiota also mediates tumor suppressive effect by inactivation of carcinogenesis via generation of short-chain fatty acids and activation of cancer-preventing phytochemicals (Schwabe and Jobin 2013) (Fig. 18.2).

## 18.4 Risk Factors of Specific Cancers

Numerous propensities especially lifestyle and diet stand as the risk factors for the changes in the microbial diversity of the gut, thus affecting the microenvironment of host's cells (Moskal et al. 2016). It is still not clear whether the shift in population pattern causes carcinogenesis or is an outcome of the emergence of tumors. Hence, this important variation will be the epicenter of research in cancer–microbiome area in the upcoming future. Different types of cancer and their association with microbiome are discussed below.

### 18.4.1 Oral and Gastric Cancer

Oral cavity is inhabited by a variety of bacterial species, which play a leading role in the development of oral diseases (Al-Hebshi et al. 2017). Dysbiosis in the oral microflora destabilizes the defense mechanisms of the host, resulting in chronic periodontal disease (Bullon et al. 2014; Johannsen et al. 2014), which is related to changes in the oral microflora that is caused by the outgrowth of certain pathogenic microbes. The two notable pathogenic members of the oral microbiome that are known to induce tumorogenesis in the oral cavity are *Fusobacterium nucleatum* and *Prevotella gingivalis* (Mager et al. 2005). Repeated periodontitis is considered to increase risk for the development of oral squamous cell carcinoma (OSCC) and *Prevotella intermedia* and *Porphyromonas gingivalis* are associated with the occurrence of periodontitis (Mysak et al. 2014; Zhang et al. 2017; Hsiao et al. 2018, Li et al. 2019). Human papillomavirus (HPV) type 16 has also been recognized as a causative agent for oropharyngeal cancer (Bray et al. 2018).

Infection caused by *P. gingivalis* has been related to increase in oral cancer, oro-digestive cancer, and propagation of oral cancer stem cells. *P. gingivalis* infection tempers with many anti-apoptotic pathways and also spreads inter-cellularly with the help of actin-based membrane protrusions and interferes with various cell signaling pathways (Mao et al. 2007; Yilmaz et al. 2004). Firstly, *P. gingivalis* activates Jak1/Akt/Stat3 signaling, which controls intrinsic mitochondrial apoptosis pathways (Mao et al. 2007; Yilmaz et al. 2004). It inhibits gingival epithelial cell apoptosis induced by ATP ligation of P2X7 receptors (Yilmaz et al. 2008). *P. gingivalis* also causes reduction in amount of p53 and accelerates the progression through the S-phase of the cell cycle (Kuboniwa et al. 2008). It promotes the expression of the B7-H1, which accelerates regulatory T-cell production and B7-DC receptors in primary gingival epithelial cells (Groeger et al. 2011). This may be the possible reason that B7-H1 expression contributes to immune evasion by oral cancers. AR2/NF-KB pathways are activated by *P. gingivalis* infection, which in turn induces expression of promatrix metalloproteinase (proMMP-9) (Inaba et al. 2014). *P. gingivalis* produces gingipains and cysteine proteinases, which play a key role in engaging the PAR2 receptor and also cleave the MMP-9 pro-enzyme into an active form. The active form of MMP-9 along with extracellular matrix degrades the basement membrane. This promotes carcinoma, cell migration, and invasion. The *P. gingivalis* might contribute to oral squamous cell carcinoma metastasis. The another pathogenic member *Fusobacterium nucleatum* works by activating inflammatory cytokines like TNF-α, IL-1β, and IL-6. Several antiapoptotic pathways are modulated by *F. nucleatum,* and it also activates p38, which results in the secretion of MMP-9 and MMP-13 (collagenase 3).

Role of human papilloma virus in carcinogenesis has been confirmed since the discovery of HPV16. HPV16 expresses E6 and E7 proteins, which further lead to the inactivation of tumor suppressor proteins p53 and Rb (Wiest et al. 2002). Inactivation of p53 and Rb causes dysregulation of host DNA synthesis, as a consequence cell cycle control is lost (D'Souza et al. 2007). This leads to destabilization of the genome, chromosomal aberrations, and abnormal centrosome numbers. HPV acts as

an independent risk factor for the development of oral squamous cell carcinoma (Duensing et al. 2000).

#### 18.4.1.1 GI Tract Cancer

Gastric cancer has been acknowledged as the model to study bacterial cancers. *Helicobacter pylori* in the gastrointestinal tract has been classified as a class I carcinogen by the International Agency for Research on Cancer (International Agency for Research on Cancer 1994). Strong host immune response is generated due to infection with *H. pylori,* which results in various gastric problems such as gastric inflammation, dysplasia, achlorhydria, and epithelial atrophy (Blaser and Atherton 2004). The key hallmarks of cancer driven by *H. pylori* include inflammation that promotes tumor, downregulation of antitumor immune destruction, and increase in proliferative signaling (Asano et al. 2015). *H. pylori* is able to adhere to gastric epithelial cells with the help of multiple adhesins, including SabA and BabA (Ilver et al. 1998). Once it firmly associates with the gastric epithelium, it deposits CagA and other virulence factors on human cells by utilizing its type IV secretion system. SHP2, a host oncoprotein, gets dysregulated by CagA after entering the cell leading to uncontrolled cell growth and motility (Murata-Kamiya et al. 2010). Other virulence factors such as VacA are responsible for making pores in host membranes, causing cell death and higher rates of cell turnover (Cover and Blanke 2005). Neutrophils and macrophages start producing reactive oxygen species (ROS) due to *H. pylori* infection (Tsugawa et al. 2012; Sung et al. 2022; Kuo et al. 2022). Inflammatory cytokines, including IL-1β, tumor necrosis factor-α, and IL-8, are also produced by *H. pylori* infection, ultimately leading to induction of Th1 immune behavior in the gut (Handa et al. 2011; Wei et al. 2010). NF-κB levels rise in patients with infection, which further drive inflammatory mechanisms of tumor initiation and succession. *H. pylori* is protected from ROS due to the presence of catalase and superoxide dismutase proteins but bystander effect damages host tissues (Chaturvedi et al. 2011). VacA, virulence factor of the pathogen, obstructs nuclear factor of activated T-cell (NFAT) activation in T cells. Blocking of NFAT leads to a deficiency of IL-2-driven T-cell proliferation, which would gradually result in expulsion of *H. pylori* (Jain et al. 2011). γ-glutamyltranspeptidase (GGT) produced by *H. pylori* also has the ability to block T-cell proliferation. Hence, a perfect storm is generated by the combination of cellular damage, innate procarcinogenic signals, and reduced immune surveillance in patients, which results in cancer.

### 18.4.2 Hepatic and Pancreatic Cancer

Hepatocellular carcinoma (HCC) is responsible for 80–90% of liver cancers and stands as the third leading cause of cancer-related deaths (Mima et al. 2017; Tong et al. 2011). Fox et al. (2010) observed the presence of *Helicobacter* spp. in gastric mucosa, leading to an increase in the chances of tumor progression in the hepatobiliary tract. *H. pylori* seizes in the host's cells by attaching to gastric epithelial cells by HopQ protein, which binds to carcinoembryonic antigen-related cell

adhesion molecules (CEACAM) and destructs the antitumor immune system, further inducing tumorigenic inflammation (Schwabe and Jobin 2013). Murphy et al. (2014) studied the association of fifteen *H. pylori* proteins with hepatobiliary carcinoma using a multiplex serology panel and found an increase in antibodies against these proteins, predicting an increase in HCC and biliary tract cancer. *Helicobacter hepaticus* also promotes HCC by producing toxins that promote anti-apoptotic factors and activate nuclear factor kappa B (NF- κB) and WNT signaling pathways, thus promoting tumor-inducing metabolites and suppressing antitumor immunity (Fox et al. 2010; Beyoğlu and Idle 2022). Other experimental studies have shown the enrichment of *Methylophilaceae*, *Fusobacterium*, *Prevotella*, *Actinomyces*, and *Novosphingobium* along with *Helicobacter pylori* in extrahepatic carcinoma tissue specimens of 100 patients (Avilés-Jiménez et al. 2016).

Similarly, highly lethal pancreatic cancer is also influenced by gut microbiota, which induces oncogenic metabolites for tumor development. Pancreatic cancer has been found to be associated with periodontal diseases and gum inflammation (Michaud et al. 2007; Stolzenberg-Solomon et al. 2003). In a comparative study of salivary microbiome of pancreatic cancer patients and healthy people, *Neisseria elongata* and *Streptococcus mitis* were found to be associated with cancer (Farrell et al. 2012; Herremans et al. 2022). Another oral bacteria, *Fusobacterium* spp., was found to be present in the tumor tissues of 283 pancreatic ductal adenocarcinoma patients (Mitsuhashi et al. 2015). *Fusobacterium* increases the inflammatory cytokines and reactive oxygen species (ROS), which leads to epigenetic alteration of mismatch proteins such as mutL homolog 1 and CpG island methylator phenotype (tumor suppressor gene), thus promoting carcinogenesis (Kostic et al. 2013; Schetter et al. 2010). *Helicobacter* spp. has also been found to be associated with pancreatic cancer (Nilsson et al. 2002; Trikudanathan et al. 2011). Evidence from different studies suggests that the accumulation of specific microbes can lead to the activation of carcinogenic factors producing hepatocellular and pancreatic carcinoma. *Prevotella* sp., *Bacteroides, Ruminococcus, Faecalibacterium,* and *Ruminiclostridium* are involved in progression of hepatic cancer (Hu et al. 2020; Yu et al. 2017). The gut microbiota may impact not only the formation of tumor but also the adequacy of chemotherapies and immunotherapies for HCC and pancreatic medical procedure, leading to low survival rates of cancer patients (Mima et al. 2017).

### 18.4.3 Colorectal Cancer

Colorectal carcinoma (CRC) being the third most malignant tumor with high occurrence in Western countries stands as the fourth most common cause for cancer-related deaths with mortality rate of 9.2% (Mármol et al. 2017; Zhou et al. 2020b, b). 70% of the human microbiome is present in the colon, which makes it the most vigorously colonized part of the gastrointestinal system (Saus et al. 2019). The modulation of colonic flora can be responsible for the dysplasia and can cause colonic inflammation and biosynthesis of carcinogenic molecules, leading to CRC

development (Arthur et al. 2012; Rubinstein et al. 2013). *Fusobacterium nucleatum*, *Peptostreptococcus stomatis, Peptostreptococcus anaerobius,* and *Bacteroides fragilis* along with twenty other microbial gene markers were found to be associated with CRC (Yu et al. 2017; Zhou et al. 2020b, b). On the other hand, the commonly found *Escherichia coli* can have the pathogenicity island (*pks*), which can synthesize colibactin, a genotoxin causing oncogenic mutations and DNA damage (Pleguezuelos-Manzano et al. 2020) (Fig. 18.1c). A polyamine catabolic enzyme, spermine, is highly inducible by inflammatory stimuli of enterotoxigenic *Bacteroides fragilis,* which results in DNA damage and increase in ROS, leading to colorectal carcinoma (Goodwin et al. 2011) (Fig. 18.1d). It is also known to produce another inflammatory toxin that causes diarrhea and colonizes in host, which can further induce CRC (Wu et al. 2009). *Enterococcus faecalis* also have capability to produce enterotoxins and ROS, causing inflammation and epithelial damage (Saus et al. 2019). The microbes alter the signaling pathway by producing toxic proteins or biochemicals, which creates unfavorable microenvironment for cells and promotes carcinogenesis. For instance, FasA surface protein produced by *Fusobacterium nucleatum* adheres to the epithelial walls of colon and interacts with E-cadherin (Zhou et al. 2022). The complex then alters the β-catenin and Wnt signaling pathways. Increase in FadA protein leads to increase in the inflammatory and oncogenic genes (Kostic et al. 2013; Rubinstein et al. 2013). Other bacterial species such as *Bacteroides, Parabacteroides*, *Lachnospiraceae bacterium,* and *Alistipes* spp. has high prevalence in CRC patients and are found to play role in development of colon carcinoma (Feng et al. 2015).

## 18.5 Role of Microbiome in Treatment of Cancer and Future Applications

Since certain microbial signatures are known to promote the development of cancer and affect the safety, tolerability, and effectiveness of treatments, there is growing evidence that the gut microbiome is connected to cancer in a variety of ways. From over past few years, tremendous progress has been made in the field of cancer treatment, but somehow the tumor microenvironment has a significant impact on how well tumor immunotherapy works. Studies have demonstrated that a variety of tumor microenvironment cells, including T cells, fibroblasts, natural killer (NK) cells, dendritic cells (DCs), and others, play a key role in tumor immunotherapy (Ferlazzo et al. 2004). NK cells additionally induce cDC1 to enter the tumor microenvironment (TME) and assist tumor immune control (Poutahidis and Erdman 2016; Zhang et al. 2018; Böttcher et al. 2018; Zhou et al. 2020b, b). Chemotherapy or immune checkpoint inhibitor resistance is linked to altered gut flora immune checkpoint inhibitors (ICIs). The antitumor effects of chemotherapy medicines or ICIs may be enhanced by altering the microbiota through the use of antibiotics, probiotics, fecal microbiota transplants, or nanotechnologies (Cheng et al. 2020).

### 18.5.1 Immunotherapy

The term "immunotherapy or immuno-anticancer treatments" refers to a variety of therapeutic modalities intended to stimulate a patient's immune system or recruit external immunological cells to combat cancer. Immunotherapy achieves the goal of eradicating cancers by inhibiting negative immune regulatory factors, stimulating the immune system, and improving immune cell identification, which results in the death of immune cells to tumors (Beatty and Gladney 2015).

In comparison with conventional cancer treatments, the gut microbiota has a stronger anti-cancer effect and further activates the host immune system. Additionally, there is growing acknowledgment for the role that the interaction between the gut microbiota and cancer ICIs plays in antitumor immune therapy, which is a form of targeted therapy for cancer immunotherapy (Qiu et al. 2021). Numerous species, including *Bifidobacterium breve* and *Bifidobacterium longum*, have been shown to improve dendritic cell activity and therefore trigger CD8+ T-cell priming and accumulation in tumor microenvironments (Tanoue et al. 2019; Sivan et al. 2015). In the tumor microenvironment, molecular cell refinement and immunological control of therapeutic targets are growing, and clinical application is expanding as well, such would be the resistance to the programmed cell death ligand 1, which plays a very crucial role in anti-tumor immunotherapy. The reduced programmed cell death ligand 1 activity that is resistant to the tumor can have favorable therapeutic effects and may be used for modifying the inert tumor microenvironment in future too (Qiu et al. 2021). Resistance to PD-1/PD-L1 plays many roles in tumor immunotherapy. Using an acceptable and selective combination of immunotherapy in a constrained tumor microenvironment reactivates the anti-tumor immune response in the host. This refers to the possibility of immune toxicity and immunotherapy to increase antitumor immunity (Ngiow and Young 2020). Antibodies that are able to act against the ligands of the PD-1 and CTLA-4 may inhibit affinity of T lymphocytes with their suppressive two or more ligands, which will act on the tumor cells, which in turn will activate the anti-tumor response in the immune system against the tumor cells (Cullin et al. 2021) (Fig. 18.3).

### 18.5.2 Chemotherapy

Chemotherapy refers to the treatment that requires anti-cancer drugs with high and powerful chemical content to treat any form of cancer by targeting the fast multiplying or growing cancer cells in the body. Chemotherapy causes DNA and non-DNA damage that is ROS-mediated, which allows bacteria to pass the intestinal epithelium. In turn, this causes an inflammatory reaction and may result in systemic infections (Kalasabail et al. 2021). The gut microbiota can influence how the body reacts to chemotherapy by enhancing medication efficacy, encouraging chemoresistance, and/or mediating adverse effects and toxicity.

Gut microbiota uses various mechanisms to regulate or modify the potency of the anti-cancer drugs. Many species of bacteria that are present in the gut impact the

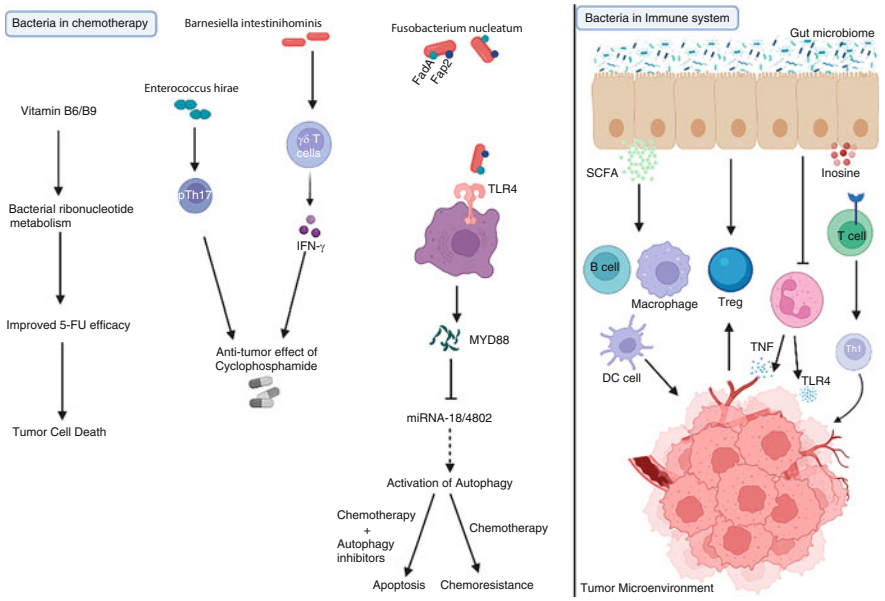


**Fig. 18.3** Role of gut microbiota in modulating efficacy of anticancer drug in cancer therapy

competency of the drugs that are used in chemotherapy and immunotherapy, which also includes immune checkpoint inhibitors by various mechanisms (Cullin et al. 2021).

*Fusobacterium nucleatum* is one such bacterium found in the gut microbiota and with the use of antibiotics/drugs can also reduce the intensity of cancer. *F. nucleatum* functions via myeloid differentiation primary response 88(MYD88) and Toll-like receptors (TLR4), which further results in the selective deprivation of miR-18a and miR-4802, and this in turn initiates autophagy. This process can further assist in chemoresistance in cancer patients (Fig. 18.3).

An earlier research demonstrated that cyclophosphamide can alter the composition of the gut microbiota by causing some gram-positive bacteria to translocate into the secondary lymphoid organs, which in turn triggers the production of "pathogenic" T helper 17 (pTh17) cells and improves the host immune response brought on by memory T helper 1 (Th1) cells. Researchers using *Caenorhabditis elegans* models have also identified bacteria that play role in chemotherapeutic effectiveness, particularly in the metabolism of ribonucleotides and vitamins B6 and B9 (Scott et al. 2017; García-González et al. 2017), which further increase the efficacy of fluoropyrimidine, an antimetabolite by inhibiting bacterial deoxynucleotide metabolism (Cheng et al. 2020). Efficacy of chemotherapy drugs can be modulated by bacteria via different mechanisms. The efficiency of 5-FU can be modulated via B6, B9, and ribonucleotide metabolism. The efficiency of 5-FU was promoted by inhibiting bacterial deoxynucleotide metabolism (Fig. 18.3).

Cyclophosphamide (CTX), one of the most often prescribed chemotherapy medications for the treatment of solid tumors and lymphomas, stimulates immunogenic cancer cell apoptosis and immunomodulatory effects (Qiu et al. 2021). Daillère et al. (2016) showed the incorporation of *E. hirae* in mice treated with antibiotics and reverses cyclophosphamide chemoresistance, which promotes pTh-17 production and T-helper (Th)-1 cell differentiation by increasing CD8+ T cells and CD4+ T regulatory cell (Treg) in the intratumoral region (Fig. 18.3). As *Barnesiella intestinihominis* builds up in the colon, it activates Th1 and polyfunctional CD8+ cytotoxic T cells in the body, which encourages interferon (IFN)-producing γδT cells to invade tumors (Daillère et al. 2016; Cheng et al. 2020) on treatment with cyclophosphamide (Cheng et al. 2020) (Fig. 18.3). Non-enterotoxigenic *B. fragilis* and *Erysipelotrichaceae* are examples of immunogenic bacteria that promote migratory dendritic cells (DCs), which then promote follicular T helper (TFH) cells through interleukin (IL) 1 and IL-12. The increased IgG2b response from stimulated TFH cells then interacts with B cells to boost the antitumor effector or the memory CD8+ T-cell activity. The response is further enhanced in the presence of gut commensal and boosts antineoplastic drugs like oxaliplatin and cisplatin (Roberti et al. 2020).

### 18.5.3 Radiotherapy

Radiation therapy is a part of the treatment plans for more than 50% of patients with cancer, and it is thought to make up around 40% of therapeutic protocols with efficacy in more than 90% of cases particularly those in their first stage of diseases (Poonacha et al. 2022). The predominantly most significant impediment to malignant cancer cure in patients is radiation enteropathy and radiation toxicity (Hauer-Jensen et al. 2014). RT also affects the gut microbiota; however, only a few studies have attempted to examine the connection between the microbiota and radiotherapy response (Tonneau et al. 2021). In melanoma, lung, and cervical cancer models, an oral vancomycin-induced decrease in gram-positive gut commensals mediated by IFNg and CD8 T-cell-dependent pathways was linked to improved radiation efficiency (Uribe-Herranz et al. 2020). Cui et al. (2017) showed the benefits of fecal microbiota transplantation (FMT) against total body irradiation-induced acute radiation enteritis in the mouse model with an increase in microbiota diversity. Irradiated mice that received (FMT) survived longer and had enhanced digestive system performance and increased levels of peripheral white blood cells. An evaluation of FMT in the treatment of chronic radiation enteritis showed a radical shift in diversifying the microbiome composition and reducing gastrointestinal symptoms (Ding et al. 2020).

### 18.5.4 Targeting Microbiome for Therapeutic Modulation of Carcinogenesis

Gut microbiota influences the shape of the tumor microenvironment by acting on the host immune system. TLR4 signaling in tumor cells recruit neutrophils, and they release tumor necrosis factor (TNF), which causes metastasis. Gut microbiota reduces the number of neutrophils, and its metabolites inosine promotes differentiation of Th1 cells in the presence of exogenous interferon-γ. An additional therapeutic option might be the introduction of anaerobic bacteria since they colonize all tumor sites regardless of oxygenation level and can even eradicate hypoxic cancers (Riehl et al. 2019; Poonacha et al. 2022). Through anaerobic action, butyrate-producing bacteria can degrade polysaccharides to create short-chain fatty acids (SCFAs), which are crucial for reducing the proliferation of cancer cells (Wang et al. 2019; Wagner et al. 2018). SCFAs like butyrate along with metabolites of tryptophan lessen pro-inflammatory cytokines and encourage the release of anti-inflammatory cytokines and affect the class conversion of B-cells, activating dendritic cells and macrophages, which affect differentiation of memory T cells, which helps limit radiation-related toxicity (Fish et al. 2016; Badgeley et al. 2021; Cheng et al. 2020) (Fig. 18.3). An introduction of *Bifidobacterium infantis*, a commensal bacterium to mice, and *B. infantis* with monoclonal antibody along with RT shows improvement in tumor cell proliferation, decreases blood supply, and enhanced cell apoptosis of the tumor. Furthermore, mice that received the combination therapy showed a higher survival rate than mice that received either the RT or a bacterial antibody alone (Du et al. 2018). Similarly, the symbiotic introduction of *Lactobacillus rhamnosus* (ATCC 7469) exopolysaccharides (EPS) in rat models with a dose of ionizing radiation was tested to slow colorectal development, enhanced the modulation of signaling growth factors involved in inflammation, and also reduced the progression of colorectal carcinoma in mice when compared to untreated control or those given *L. rhamnosus* or irradiation alone (Ruiz-Ruiz et al. 2017). These findings regarding the significance of the unique characteristics of the patient's pre-existing microbiota suggest the possibility of incorporating microbiota analysis into personalized treatment protocols to predict how therapy will affect the patient and how the gut microbiota can be used as a biodosimeter to check the biological response for treatment planning (González-Mercado et al. 2021; Shi et al. 2020; Ding et al. 2020).

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