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Infectious Agents and Cancer

REVIEW

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Gastrointestinal cancer resistance to treatment: the role of microbiota

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Abstract

The most common illnesses that adversely influence human health globally are gastrointestinal malignancies. The prevalence of gastrointestinal cancers (GICs) is relatively high, and the majority of patients receive ineffective care since they are discovered at an advanced stage of the disease. A major component of the human body is thought to be the microbiota of the gastrointestinal tract and the genes that make up the microbiome. The gut microbiota includes more than 3000 diverse species and billions of microbes. Each of them has benefits and drawbacks and been demonstrated to alter anticancer medication efficacy. Treatment of GIC with the help of the gut bacteria is effective while changes in the gut microbiome which is linked to resistance immunotherapy or chemotherapy. Despite significant studies and findings in this field, more research on the interactions between microbiota and response to treatment in GIC are needed to help researchers provide more effective therapeutic strategies with fewer treatment complication. In this review, we examine the effect of the human microbiota on anti-cancer management, including chemotherapy, immunotherapy, and radiotherapy.

Keywords Gastrointestinal cancer, Microbiota, Chemotherapy, Immunotherapy, Radiotherapy

Introduction

Gastrointestinal (GI) cancers, including malignancies of the esophagus, stomach, and colorectum, are among the most frequently occurring cancers in humans. Although they arise from distinct origins, these cancers display diverse clinical characteristics, while also sharing certain similarities [1]. The incidence of cancer caused by carcinogenic infections currently accounts for approximately 10–20% of new cancer cases. However, this percentage is anticipated to rise in the future as researchers delve deeper into the field of cancer microbiome research. Through these studies, scientists are gaining a better understanding of how tumor-associated microbes play a significant role in the initiation and progression of cancer, as well as their potential to develop resistance against treatment methods [2].

The human microbiota, consisting of trillions of cells such as bacteria, viruses, and fungi, is widely acknowledged for its influence on human well-being and illness. There are many different kinds of bacteria in the human microbiome. Including commensal, symbiotic, and pathogenic species, that inhabit various parts of the body such as the skin, oral cavity, and GI tract [3, 4]. The gut harbors the most abundant microbial community, which has prompted extensive research to comprehend the effects of gastrointestinal microbiota on various diseases [3]. This effect is achieved by a variety of mechanisms, including DNA damage, activation of oncogenic pathways, creation of carcinogenic metabolites, spure of chronic inflammation, and suppression of the body's

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antitumor immunological responses. These mechanisms collectively contribute to the role played by carcinogenic infections in the development and progression of cancer [5].

A considerable body of preclinical research, along with several clinical studies, highlights the crucial role of gut bacteria in modulating the host's response to antitumor drugs, specifically conventional chemotherapy, and immunotherapy. Current findings emphasize the importance of gut microbiota in determining the efficacy and outcomes of current treatment modalities [6]. This review focuses on understanding the role of bacteria in GIC and explores how altering the microbiota can impact the effectiveness of various anticancer treatments, including conventional chemotherapy, immunotherapy, radiotherapy, and oncological surgery.

Overview on gastrointestinal *cancer*

Malignant tumors of the digestive tract and supporting organs, including colorectal, esophageal, gastric, and ampulla carcinomas, are referred to as "gastrointestinal cancers" (GICs) [7]. Development of the colorectum, stomach, and pancreas cancers are the most common gastrointestinal cancers reported throughout the Western world, including the United States [8]. Based on accumulating evidence, GIC have possibly been most comprehensively studied and molecularly characterized among solid cancers in the last two decades.

Gastric cancer

The World Health Organization has identified gastric cancer (GC) as a public health problem due to the almost one million new cases of the disease reported each year, which places it as the third highest cause of cancer-related deaths globally [9]. Gender, age, and race/ethnicity, are only a few of the numerous risk factors for stomach cancer that cannot be changed. Other controllable risk factors include smoking, consuming a diet high in nitrates and nitrites, and having an infection with *Helicobacter pylori*. There are a few additional extremely rare risk factors as well, such as MALT lymphoma (mucosa-associated lymphoid tissue lymphoma), having stomach surgery history, and pernicious anemia. GC in first-degree relatives adds another layer of risk. GC has been linked to a number of hereditary cancer syndromes. The hereditary diffuse gastric cancer (CDH1) condition, in which 80% of patients will develop stomach cancer, has the highest correlation [10].

Colorectal *cancer*

Being the third most prevalent cancer in terms of diagnoses and the fourth leading cause of cancer-related deaths globally, colorectal cancer (CRC) poses a serious threat to public health. Due to varying exposure to risk factors, the development and adoption of screening, as well as availability to the right kind of treatment services, there has been a significant amount of variation over time between the various geographic locations [11].

In Asia, CRC ranks third among neoplastic malignancies that affect both sexes. With the exception of non-melanoma skin cancer, it represents 9.7% of all cancer cases combined [12, 13]. Across the globe, industrialized countries account for over 50% of instances due to rapid lifestyle changes and dietary patterns. Patients over 50 or 60 upon diagnosis account for the majority of cases [14, 15]. Globally, CRC ranked fourth in 2013 for cancer-related mortality. Asia recorded the highest number of prevalent cases of CRC, although having a lower prevalence rate than other Western countries. Global cancer statistics indicate that 9.9 million deaths and 19.3 million new cases of colorectal cancer were reported in 2020 [16]. 10% of cases are new, and 9.4% of deaths are related to CRC. Globally, 1.93 million subjects have been spotted with CRC, and of none, 0.94 million will lose their lives to the disease in 2020, according to the Global CRC Burden Study Report [15]. Taking care of a patient with CRC can be costly and complicated, and it can lead to a lower quality of life, particularly if the cancer has spread. For this reason, CRC primary prevention and screening programs are essential to promoting a healthy society and saving lives [12].

Adenomatous polyps, also known as adenomas, are tissue growths carry a higher risk of cancer. The majority of colorectal malignancies start as early adenomas called aberrant crypts. When seen in the histology of a villus, this continues to grow and becomes an advanced adenoma that is larger than 1 cm [13]. Up to their hayflik limit, healthy cells proliferate and divide in an orderly manner before starting to die off. Cancer, however, divides endlessly and has no hayflik limit. The emergence of early-onset colorectal cancer (EOCRC) in individuals under 50 years of age has grown in prominence in recent times. Biologically, anatomically, metabolically, pathologically, and epidemiologically, EOCRC differs from late-onset CRC (LOCRC). By 2030, the incidence of EOCRC is predicted to rise by more than 140% [14–16].

People in developing countries who have begun to follow western diets, such as eating less fiber and more animal proteins and fat, having a previous history of CRC polyps, and inheriting syndromes passed down through generations, are just a few of the factors that increase the risk of colon cancer [13]. People over 50 are more likely to be affected by colon cancer, while those under 50 have a 4% chance [17]. Inflammatory bowel conditions, such as ulcerative colitis and Crohn's disease, as well as

Gardner, Turcot, and Peutz-Jeghers syndromes, can raise the risk of colon cancer [18].

Pancreatic cancer

With a 5-year survival rate of about 9%, pancreatic cancer is the fourth most common cause of cancer-related mortality worldwide and the deadliest gastrointestinal malignancy. Only 20% of pancreatic cancer patients are suitable for curative surgery, and the majority of patients receive their diagnosis at an advanced stage. Additionally, pancreatic cancer treatments now available do not deliver satisfying outcomes. A key characteristic of pancreatic cancer is the presence of an abundance of stroma in the tumor microenvironment (TME), which promotes tumor development, progression, and chemo resistance [19]. The tumor microenvironment of pancreatic cancer is very diverse pathologically. Blood arteries, endothelial cells, immune cells, and cancer-related fibroblasts can all be found in the stromal microenvironment of pancreatic cancer. Different patients' proportions of these factors frequently differ, which also causes variation in the prognosis and treatment outcomes for those with pancreatic cancer [20].

Therapies for gastrointestinal *cancer*

Despite significant advancements in systemic treatment for GI malignancies in recent decades, surgery is still the only therapeutic strategy that offers a definitive cure in the majority of cases. The mainstay of care for resectable stomach cancer is radical surgery. Several therapeutic techniques have been established to minimize the risk of recurrence and increase long-term survival, including perioperative chemotherapy, adjuvant chemotherapy, and adjuvant chemoradiotherapy. In addition to the decision of whether or not to proceed with surgery and the surgical technique used, postoperative care is essential to obtaining the intended results [21]. Emerging research suggests that psychological stress connected to surgery may possibly potentially cause tumor dissemination in addition to in-hospital recovery. Gastric cancer surgery account for the about 4% and 40% postoperative mortality and complication rates, respectively, and are accompanied with substantial morbidity [22].

Currently, chemotherapy and radiation are frequently used in conjunction with surgery to treat GIC [10]. According to reports from the American Cancer Society for 2020, recurrences are frequent despite extensive trimodality therapy, and globally 5 year relative survival rate range from 73 to 90% for regional or localized colorectal cancer to just 14–42% for regional or localized pancreatic cancer [23]. After main therapy, treatment intensification using adjuvant medicines has been suggested to enhance results for individuals who are most at risk of recurrence. Current prognostic techniques, however, have unfavorable drawbacks that make it difficult to accurately assess treatment response and stratify patients. Radiographic (imaging) techniques are pricy, burdensome for patients, and have a limited range of detection [24].

Adjuvant chemotherapy is advised in combination to surgery to eliminate micro metastasis after curative resection surgery. When colon cancer patients are receiving adjuvant treatment with nodes positive, the efficacy of adjuvant chemotherapy has been amply demonstrated [25]. Numerous research have reported on the effects of adjuvant chemotherapy in colon cancer patients in stages II and III. Recently also sees the publication of guidelines for individuals with resected stage II colon cancer who should get adjuvant chemotherapy [26–30].

Neoadjuvant therapy may also increase survival in patients with resectable and borderline resectable pancreatic cancer compared to upfront surgery, however high-quality information is missing in this area [30]. The recommended course of treatment for resectable pancreatic cancer is resection followed by adjuvant chemotherapy. The National Comprehensive Cancer Network guidelines encourage neoadjuvant therapy for pancreatic cancer that is borderline resectable, whereas NICE recommendations only support it when it is a part of a clinical study. Both guidelines contain suggestions without a basis in randomized controlled trials (RCTs). Compared to neoadjuvant therapy, upfront surgery with adjuvant therapy may have advantages. The first option is to skip biliary stenting for obstructive jaundice [31, 32].

Additionally, chemotherapy patients do not run the danger of preoperative clinical deterioration. Last but not least, neoadjuvant therapy postpones surgery and tumors resistant to chemotherapy may develop and become unresectable. The advantage of neoadjuvant therapy is that systemic chemotherapy will always be administered as soon as possible. Neoadjuvant treatment may also increase the probability of a microscopically perfect (R0) resection. Lastly, neoadjuvant therapy may prevent unnecessary surgery for people whose illnesses are rapidly worsening [30].

Photodynamic therapy (PDT) has been explored as a treatment option for GC because of its possible benefits in targeting and maybe less detrimental side effects [33]. There are numerous published studies on clinical PDT in the field of GI oncology [34, 35]. However, during clinical treatment, it was discovered that different patients responded to PDT in different ways, and even among the same individuals potentially have variable clinical results depending on when they receive treatment. Historically, additional possible effects were minimized by focusing mostly on altering the photosensitizer dose as well as the radiation's intensity and duration. PDT is occasionally

used in GC because of its ability to precisely target tumor tissue while causing little injury to neighboring healthy tissues, having few systemic adverse effects, and being repeatable. PDT has been used to treat several cancers, including esophageal, gastric, bile duct, and CRC. However, the photosensitizer, irradiation light source, and operators have a significant impact on PDT's therapeutic effectiveness [36].

Chemotherapy, radiation, and other conventional therapeutic modalities have not been successful in effectively treating cancer. Therefore, the search for novel, powerful anticancer drugs is urgent. The evidence that is now available and the encouraging results of using bacteria as anticancer agents on different cancer cell lines have piqued scientists' interest in the therapeutic potential of bacteria in the treatment of cancer [37]. Additionally, genetic engineering has been applied in various research on bacteriotherapy drugs to overcome obstacles and improve efficacy with the fewest side effects. Numerous bacterial species are employed to preferentially address the hypoxic situation of tumors, which leads to the reduction of tumor growth, whether they are live, attenuated, or genetically altered [37].

Microbiota and gastrointestinal cancer

A increasing body of research is showing how human health and disease may be impacted by the microbiota in the gut, which is every microbial population's genome that reside in the gastrointestinal system [6]. The identification and detection of an increasing number of bacteria, fungi, and viruses that can affect the host intestinal permeability, inflammatory status, and carcinogenesis has been made easier by new detection techniques such whole genome sequencing [38, 39]. Accumulating evidence has shown that, the gut bacteria perform a variety of tasks, including vitamin generation, pathogen defense, immune response stimulation, and food fermentation. More importantly, pathogenic microorganisms might negatively impact how cancer develops and is treated [40]. A less stable, more diversified, and more pathogenic microbiota is known as gut dysbiosis. It arises when the delicate balance of the microecosystem in the gastrointestinal tract is upset. This disorder impairs the organism's physiological functions, which leads to a plethora of pathological disorders [41]. Numerous pathways of cancer mediated by dysbiosis of the microbiota have also been hypothesized recently (Fig. 1).

Based on research, roughly 15–20% of malignancies are supposed to be caused by particular infectious pathogens, whereas other malignancies are associated with the total gut microbiota, with or without the participation of specific trigger bacteria. The microbiome's influence on the risk of cancer is multifaceted and includes effects on host metabolism, immunological response, host/microbial sensin networks, and cell division [42]. For example, carbohydrate units on gastrointestinal mucins mediate as a binding site and/or a metabolic substrate for bacteria, which are key components of the process of microbial colonization at a particular place. Microbe-induced chronic inflammation accelerates the growth and spread of cancer by promoting metastasis and tumor invasion, among other processes. Increases in pro-inflammatory cytokine levels brought on by microbes can result in epithelial DNA damage, epigenetic regulatory alterations, and genetic instability. These elements have an impact on cancer's development, spread, and treatment [42].

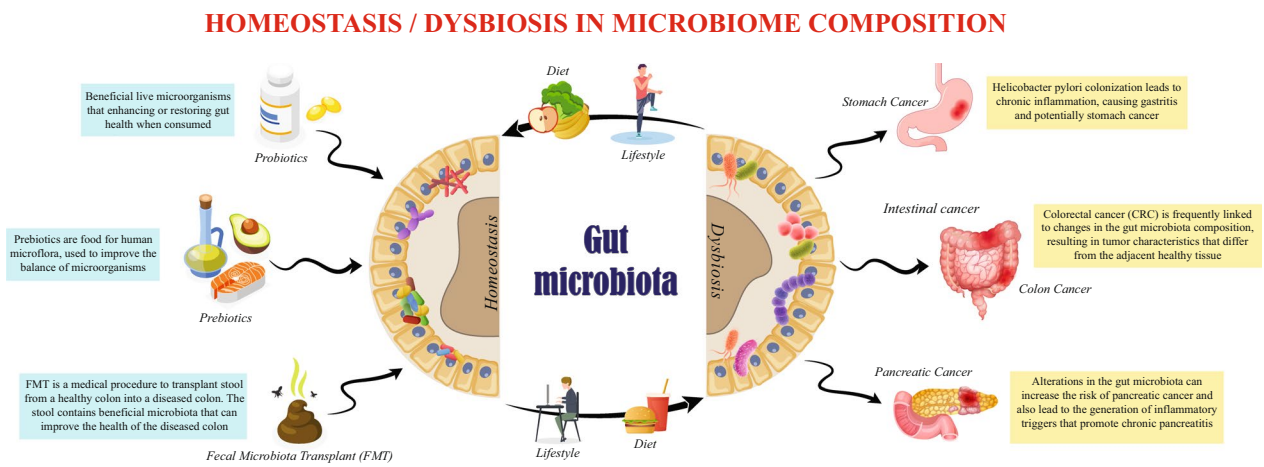

Fig. 1 Homeostasis and dysbiosis in gastrointestinal microbiome composition. In Normal individuals, microbiota–host partnership has homeostatic stability; however, slight imbalance in the composition or balance of the gastrointestinal microbiota, or dysbiosis, result in numerous gastrointestinal diseases like cancer

Microbiota and gastric cancer

The human stomach microbiome, which has been isolated using a variety of techniques, including microarrays, random shotgun sequencing, next-generation sequencing, and others, is mostly composed of five phyla: *Bacteroides*, *Actinomycetes*, *Firmicutes*, *Proteobacteria*, and *Fusobacteria* [43]. Furthermore, a number of bacteria, including *Lactobacillus*, *Streptococcus*, *Pseudomonas*, *Xanthomonas*, *Proteus*, *Klebsiella*, *Neisseria*, *E. coli*, and *Campylobacter jejuni*, have been found in the stomachs of individuals suffering from hypochlorhydria [44, 45]. An estimated 1013–1014 bacteria make up the intestinal microbiota [46]. The microbial burden in the stomach is substantially lower than that of the intestine (1010–1012 colony-forming units (CFU)/ml), at approximately 102–104 CFU/ml [47]. Firmicutes, Actinobacteria and Bacteroidetes composed the most important microbial community in gastric mucosa in normal state, while Proteobacteria and Firmicutes are common in gastric juice [43, 48, 49]. Different factors are effective in microbiome composition like mode of delivery (MOD), age, gender, nutrition, living conditions, ethnicity, use of antibiotics, and the presence of *H. pylori* [50, 51]. The majority of *H. pylori* strains have the ability to change the stomach environment, which modifies the microorganisms that live there. Changes in the gastric microbiome composition can raise the risk of GC by producing microbial metabolites, inflaming the stomach, and damaging DNA [39].

Six Swedish individuals, both with and without *H.pylori* infection, were subjected to a barcoded pyrosequencing analysis. The results showed that the gastric microbiome of the negative patients was more diversified than that of the positive patients [52]. One of the potential causes of GC in infected populations is *H.pylori*-mediated inflammation [53]. Over 50% of people worldwide suffer from *H.pylori* infection, with developing nations having a higher prevalence of the infection. Age, ethnicity, and living situation all affect the prevalence of *H.pylori* infection, with childhood being the most common age of infection [54]. *H. pylori* colonization causes chronic inflammation, which leads to gastritis and, in some cases, stomach cancer. Other stomach microbes besides *H.pylori* have also been connected to the development of GC Several investigations showed that *H.pylori* stimulates the R-catenin signaling pathway, which in turn promotes the growth of tumors. On the other hand, *H.pylori's* function in the early stages of gastric carcinogenesis is supported by the fact that its removal lowers the risk of GC in those who are infected [55]. Precancerous lesions are caused by inflammation induced by the death of epithelial cells and the repair of surviving cells, which increases cell survival and proliferation. Bacterial effectors such as cagA, vacA, and omp activate cell signaling pathways such PI3K/Akt, Ras, Raf, ERK, JAK/STAT, etc., resulting in uncontrolled cell proliferation [56]. (Fig. 2).

The PI3K/Akt/mTOR pathway is primarily responsible for mediating survival signals caused by many receptors, and it is frequently active in advanced GC [57]. Because it promotes cell proliferation and inhibits apoptosis, it has an important role in the formation and progression of tumors [58]. The three mechanisms listed below can activate the PI3K/AKT signaling pathway, which is crucial to the pathophysiology of CagA. The first one is interaction of the CM motif with the hepatocyte growth factor (HGF) receptor c-met when CagA is not phosphorylated, thereby enhancing c-Met-mediated activation of PI3K/Akt signaling through a phospholipase Cγ (PLCγ)-related junction protein. This inactivates the downstream target gene GSK-3β and induces crosstalk between the NF-κB and Wnt/β-catenin signaling pathways to enhance inflammatory response and encourage cell proliferation [59].

STAT3, also known as signal transducer and activator of transcription 3, is in charge of basal homeostasis, apoptosis, and angiogenesis proliferation all of which are indicators of the development of cancer, including GC. Growth factors and proinflammatory cytokines released by *H.pylori* as well as the activation of receptor tyrosine kinases (JAK1, JAK2, and Src) can activate STAT3 [60]. JAK/STAT signaling is essential for immune system modulation, stem cell maintenance, cell division, and proliferation. The proteins known as Janus Kinases (JAKs) are linked to the cytoplasmic domain of many transmembrane receptors, primarily cytokine receptors [61].

The Mitogen-activated protein kinases (MAPKs) are important mediators of signal transduction that controls numerous vital function like cell growth, differentiation, stress, inflammation, and immunity by sequentially activating MAPK, MAPK kinase (MEK, MKK, or MAPK kinase), and MEK kinase (MEKK, MKKK, or MAPK kinase kinase) [59]. Once CagA phosphorylated, a growth factor attaches to a tyrosine kinase receptor and generate a binding sites for the SH2 domain of SHP2 and autophosphorylation. Then, SHP2 activation triggers Ras activation, and activated Ras-GTP complex subsequently initiates the phosphorylation of Raf protein. MEK phosphorylates and activates via Raf, which in turn activates ERK. The transcription factor ELk1 is phosphorylated by active ERK once it enters the nucleus. The expression of the c-Fos and c-Jun genes occurs when SRF and activated ELK1 attach to SRE. The transcription factor ELK1-SRF complex initiates the transcription of cyclin D. Cell proliferation is caused by an increase in cyclin D. SHP2 is activated by Src activating CagA. SHP2 activation results in unchecked cell division [62].

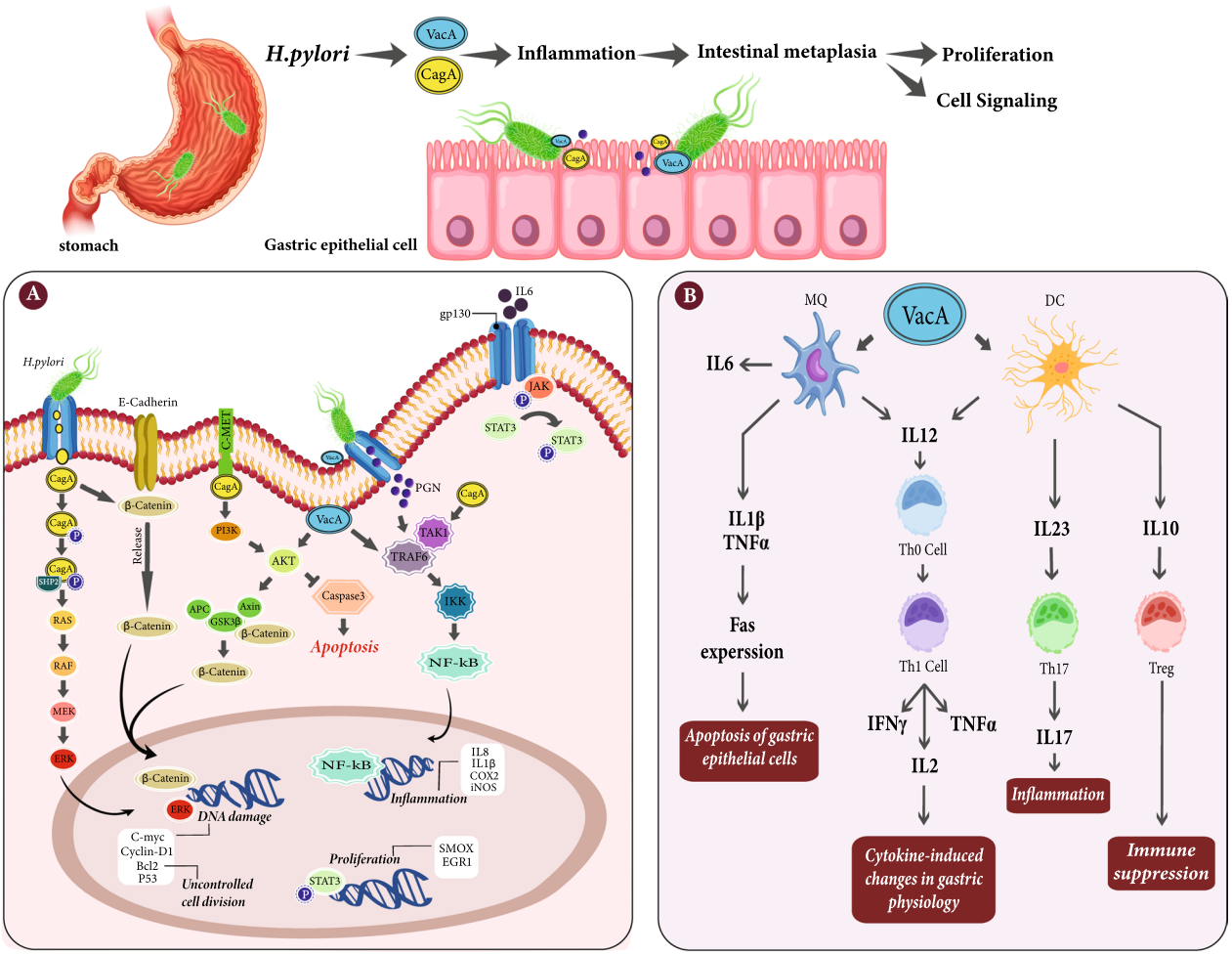

Fig. 2 Molecular and cellular features associated with helicobacter pylori-induced gastric carcinogenesis. **A** Direct impacts that cause uncontrolled cell proliferation and DNA damage are caused by bacterial effectors such cagA, vacA, and omp. CagA phosphorylation arises by host's Src/Abl kinases and the phosphorylated CagA stimulates a series of signaling molecules like PI3K/Akt, Ras, Raf, ERK, JAK/STAT, and βcatenin. **B** When the *H. pylori* reaches to submucosa, DCs capture and present the antigens to the naive T cell and define the outcome of immune responses. According to the cytokine pattern in the bacterial microenvironment, T cells differentiate into TH1 and TH17 phenotypes which induces the inflammatory response. TH17 more also induces MMPs through IL-17. In contrast, secreted IL-2 from DCs promote Tregs differentiation and in turns suppresses the effective immune responses by secreting IL-10 and so, preserving *H. pylori* inside the gastric mucosa. IL: Interleukin; TNF: Tumor necrosis factor; Cag A: Cytotoxin associated gene A; Vac A:Vacuolating cytotoxin A; JAK: Janus kinase; STAT:Signal transducer and activator of transcription; Ras:Rat sarcoma; Raf:Rapidly accelerated fibrosarcoma; ERK: Extracellular signal-regulated kinase; PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; MMPs: Matrix metalloproteinases; Omp: outer membrane protein

Matrix metalloproteinase-10 (MMP-10) is expressed by gastric epithelial cells in response to *H.pylori* and interleukin-22 (IL-22) through the extracellular signal-regulated kinase (ERK) pathway. In addition to causing inflammation by recruiting $CD8^+$ T cells and producing chemokine ligand 16 (CXCL16), MMP-10 also interferes with tight junction proteins, which damages the stomach mucosa.

Furthermore, animal models and stomach organoids show that the *H.pylori* virulence component CagA is associated with the c-Met receptor and cellular proliferation. Collectively, these investigations demonstrate how bacteria interact with several elements of the tumor microenvironment to facilitate the development of tumors [63]. VacA is a crucial virulence factor that was first discovered due to its capacity to cause vacuolation in epithelial cells. VacA is a multipurpose toxin that acts on various types of host cells, including mast cells, T cells, phagocytic cells, antigen-presenting cells, and stomach epithelial cells. VacA affects host gastric epithelial cells in a number of ways besides vacuolation, such as by causing apoptosis, increasing the permeability of the

mitochondrial membrane, and interfering with endocytic trafficking.

Moreover, VacA regulates the host immune response by preventing immune cell activation and proliferation and increasing the production of proinflammatory cytokines by mast cells (e.g., TNF-a and IL-6) to encourage the growth of GC, peptic ulcer disease, and gastritis linked to *H.pylori* [54]. During the innate immune response, inflammatory mediators are released in response to *H.pylori* virulence factors, which in turn encourages T helper (Th)1/Th17 cell responses and increases the synthesis of IFN-γ, IL-17, and TNF-α [64, 65]. Therefore, Th1/Th17 cell responses induces the chronic inflammatory state in *H.pylori*-infected patients. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) disrupt signal transduction pathways and induce DNA damage such as point mutations and double strand breaks, and cause gastric epithelial cells to undergo autophagy or apoptosis, are enhanced by *H.pylori* and the chronic inflammation it causes [66, 67]. *H.pylori* not only affects effector T cells but also triggers the host's immunosuppressive defenses. Regulatory T cells, or Tregs, suppress immune responses that are excessive or atypical and may pose a threat to the host. Tregs modulate inflammation mediated by *H.pylori* and cause the development of GC through immune responses suppression [68].

The development of GC is also aided by non-*H.pylori* bacteria while the overall data is still limited. In a high-risk area of China, a prospective randomized controlled trial showed that over a 7.5-year period, the prevalence of GC was comparable in individuals undergoing *H.pylori* eradication medication vs. a placebo. When *H.pylori* monoassociation was present in germ-free insulin-gastrin mice, it caused less severe gastric lesions and delayed the beginning of gastrointestinal intraepithelial neoplasia (GIN) compared to mice with a complex microbiome. However, it also accelerated the development of atrophic gastritis and GIN.

It was also indicated that numerous non-*H.pylori* bacteria like *Veillonella*, *Clostridium*, *Lactobacillus*, *Haemophilus*, *Neisseria*, *Nitrospirae*, and *Staphylococcus*, play a significant role in progress of GC through stimulating the production of N-nitroso compounds (NOCs) [10]. NOCs have garnered significant attention because of their ability in induction of DNA-damaging metabolites which forms cancerous lesions in epithelial cells [11]. These findings suggest that certain stomach microbes are essential to the development of GC.

Microbiota and colon cancer

Because the colon has the highest concentration of bacteria, it is one of the most extensively researched human microbial ecosystems [54]. CRC is consistently associated with altered gut microbiota profiles, with tumor signatures diverging from nearby normal tissue. As CRC advances, differences such as decreased diversity and changed community organization become more pronounced. Reduced diversity and changes in community organization become more obvious. Increase in species including *Fusobacterium*, *Bacteroides*, *Campylobacter*, *Escherichia*, *Porphyromonas Firmicutes*, *Actinobacteria phyla*, and the Lachnospiraceae family and Lower numbers of beneficial and potentially protective taxa, notably butyrate favors oncogenesis [13, 19]. Additionally, studies have revealed that a number of species, including Oscillospira, are reduced as an advanced adenoma develops into an early CRC. It is extremely difficult to determine which bacteria in the colonic microbiota are carcinogenic and how they contribute to the development of CRC; in contrast to GC, mostly caused by a single bacterium [42]. It's becoming more and more obvious that pathogens contribute to the development of colorectal cancer. Interestingly, colon harbors one million times more bacterial cells than small intestine, and the around 12 times more malignancies, implying that the gut microbiota may have a role in colorectal carcinogenesis [69]. It is well-established that healthy gut microbiota is a critical player in in CRC prevention by production of the beneficial metabolites which can have antioxidant and anti-inflammatory properties. A large-cohort multi-omics dataset showed that changes in the microbiome are made in early stages of the development of CRC, which could be of promising etiological and diagnostic status [20].

Streptococcus bovis through stimulating the production of inflammatory cytokines such as TNF-alpha, IL-1β, IL-8, and IL-6 exert its carcinogenic effect. These cytokines can produce free radicals, which can make DNA damage and cause cancer. Additionally, bacteria cause cancer by breaking down anticancer compounds like dietary tannic acid [56]. Likewise, *Bacteroides fragilis* (*B. fragilis*) can induce inflammatory reactions in the intestinal tract due to *B. fragilis* toxin (BFT) which can result in chronic intestinal inflammation and tissue injury and associated with CRC development [22]. BFT elicits colonic epithelial cells to express COX-2 in turns COX-2 cause prostaglandin E2 (PGE2) production. PGE2 modulate cell proliferation and activating oncogenic signalling pathways [21, 70]. Moreover, BFT modifies the structure and function of colon epithelial cells through degrading E-cadherin. E-cadherin's extracellular domain is broken down by BFT, and its cytoplasmic domain binds to β-catenin [30]. Elimination of E cadherin causes β-catenin signaling, c-myc, and IL-8 to be induced [56]. These signaling lead to damage to the epithelial barrier, oxidative DNA damage, and the STAT3/TH17 immune response. The contact between BFT and epithelial cells

triggers STAT3. Consequently, interleukin IL-2 levels will drop because of Tregs activation. Th17 cells are produced when IL-2 levels decline, which raises IL-17 levels. IL-17 increases the survival and growth of cancer cells and is linked to early intestinal inflammation. Moreover, increasing IL-17 secretion triggers NF-κB in the colon epithelial cells; generating the chemokines like CXCL1, CXCL2 that recruit Myeloid derived suppresser cells (MDSC), which results immune evasion [71, 72] (Fig. 3).

Escherichia coli are commonly found in the colonic mucosa of patients with CRC. *Escherichia coli's* involvement in CRC is due to the production of genes like Colibactin which is made by the pks pathogenicity island and is made up of the gene cluster clbA–clbs [73]. That damage DNA and interfere with the cell cycle and Long-term inflammation and its possible effects on DNA repair by downregulation of DNA mismatch repair proteins [56].

Fusobacterium nucleatum (*F.nucleatum*)is frequently detected in combination with other oral cavity commensal microorganisms, such as *Peptostreptococcus*, *Leptotrichia*, and *Campylobacter* species, in CRC, both

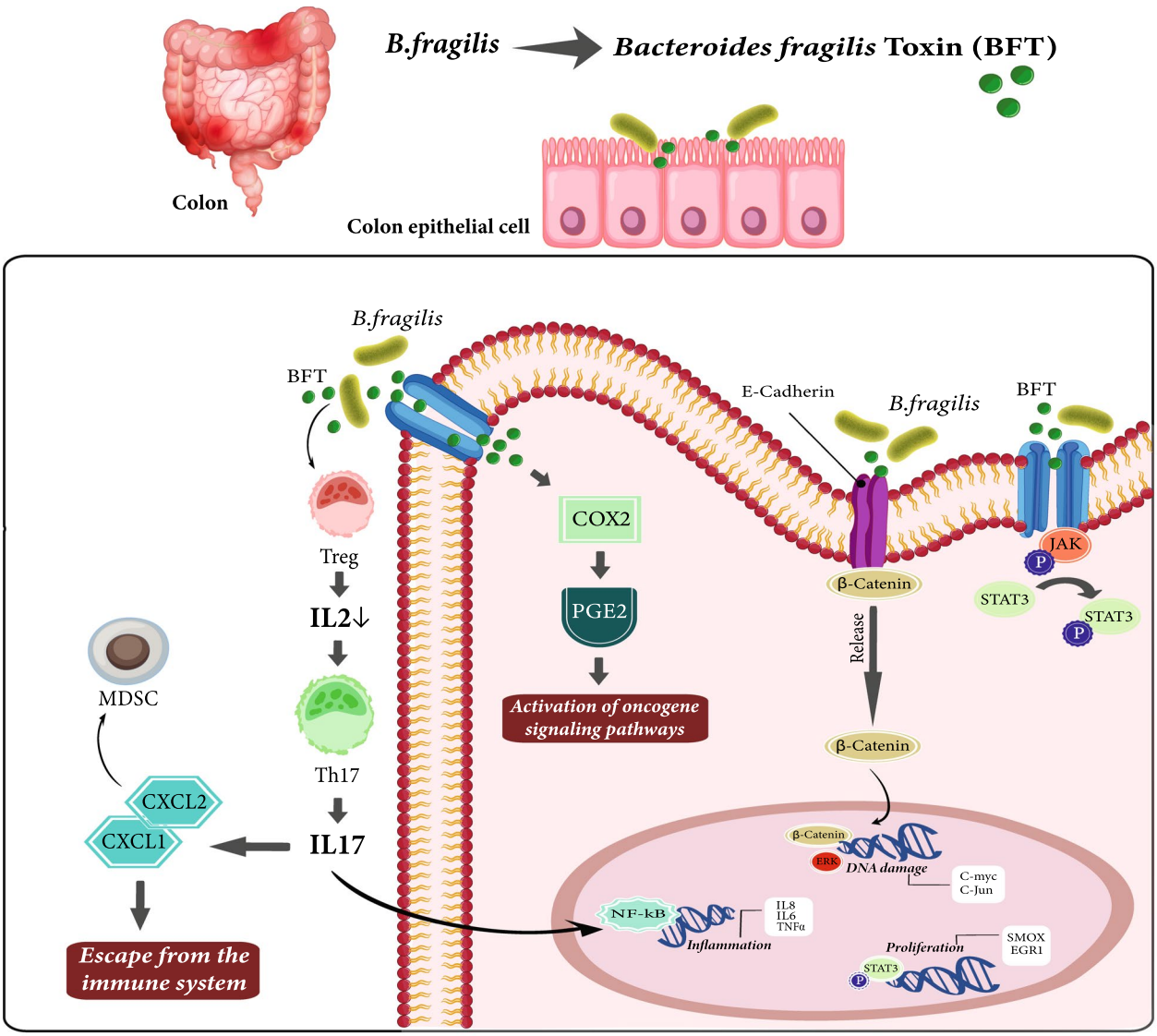

Fig. 3 Mechanisms of *Bacteroides fragilis* in colon carcinogenesis. BFT toxin is considered the main agent in ETBF carcinogenesis in colonic epithelium. This toxin stimulates β catenin by cutting E-cadherin, which leads to cellular proliferation. BFT also promote Th17 lymphocytes polarization, activation NF-κB, producing chemokines that recruit MDSC. This results immune evasion and promote carcinogenesis. BFT: Bacteroides fragilis toxin; ETBF: Enterotoxigenic Bacteroides fragilis; E-cadherin: Epithelial cadherin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; MDSC: Myeloid-derived suppressor cell

at the adenoma and adenocarcinoma stages. Moreover, the development of chemo resistance and a higher risk of CRC recurrence are linked to its existence. Through its capacity to localize with tumor-enriched lectins via the outer membrane protein, *F.nucleatum* frequently is detected at higher levels in the tumor microenvironment. *F.nucleatum* also modifies the tumor microenvironment by inhibiting natural killer cell (NK) antitumor responses and directing myeloid cell recruitment. As evidenced by the identification of microbiome profiles linked to Fusobacterium-enriched but not Fusobacterium-negative malignancies in distant metastases, *F.nucleatum* also affects the microbial metastatic dissemination [42].

Microbiota and pancreatic *cancer*

Recent data emphasizes the significance of the gut microbiota in human pancreatic disorders such pancreatitis and PDAC (pancreatic ductal adenocarcinoma). Numerous bacterial metabolites may play a role in the control of pancreatic cancer development, immunological function, and drug resistance. The TME of PDAC has also revealed intratumoral microorganisms. An important discovery in understanding the changing efficacy of chemotherapeutic drugs and immunotherapies against PDAC may be the interplay between the host microbiome and therapeutic efficacy [74]. A risk factor for pancreatic cancer, changes in the gut microbiota can also produce inflammatory stimuli that favor the development of chronic pancreatitis [75].

Numerous studies revealed variations in the gut microbiota between healthy controls and PDAC patients. Patients with PDAC have a less diverse gut microbiota and a distinct microbial profile, with a decrease in some probiotics like *Bifidobacterium* and butyrate-producing bacteria like *Coprococcus*, *Clostridium IV*, *Blatuia*, *Flavonifractor*, and *Anaerostipes*, and an increase in potential pathogens like *Enterobacteriaceae*, *Veillonellaceae*, *Streptococcaceae* and LPS-producing bacteria like *Prevotella*, *Hallella*, and *Enterobacter* [76]. Another study confirmed that PDAC patients' duodenal fluid contained less alpha diversity than age-matched individuals with normal pancreas and pancreatic cysts [76].

Several studies have been done on how the gut microbiota affects pancreatic function and disease. Bacterial translocation is prevented by the pancreatic ductal epithelium's tight connections and the release of antimicrobial peptides. The pancreatic parenchyma may, however, become opportunistically colonized if the equilibrium between the gut microbiota and the pancreatic barriers is altered. Additionally, tiny compounds and toxins originating from a disturbed gut microbiota could have an indirect impact on the pancreas in addition to directly colonizing it with bacteria. Acute, chronic, and autoimmune pancreatitis are three types of inflammatory pancreatic illnesses that are still linked to significant death and morbidity rates. Both acute and chronic pancreatitis cause a systemic inflammatory and immunological response in addition to being a local disease. Undoubtedly, dysbiosis, the gut microbiota, and the development of acute pancreatitis are closely related [76]. According to research, *Porphyromonas gingivalis* is associated with an increased risk of pancreatic cancer. Although reported as an oral bacteria, it has been discovered as an intracellular pathogen in human pancreatic cancer. In hypoxic conditions, the intracellular persistence of *P.gingivalis* is increased, which is a key feature of pancreatic cancer, and intracellular residency is directly associated to increased proliferation of malignant cells [36].

Microbitoa and chemotherapy

The microbiota demonstrates a diverse range of enzymatic activities that impact the way chemotherapy reacts and its potential for causing toxicity. Growing understanding substantiates the capacity of primarily bacteria-derived enzymes to interact with chemical compounds like chemotherapy medications. Beyond its traditional role in maintaining host well-being, the profound impact of microbiota on chemotherapy outcomes has gained significant attention [77].

One of the notable aspects of this interplay is the microbiota's capacity to influence the efficacy of chemotherapy treatments. Recent studies underscore how the body's metabolism and accessibility to chemotherapy drugs can be significantly impacted by the makeup of the gut flora. Consequently, this can affect the pharmacokinetics of these agents and ultimately impact their therapeutic potential. As an illustration, around 30–40% of individuals undergoing irinotecan treatment encounter severe mucositis, often resulting in a decrease in drug dosage or early discontinuation of the therapy [78, 79].

Additionally, the role of microbiota in modulating the host's immune responses adds complexity to the relationship, potentially augmenting or diminishing the desired anti-tumor effects of chemotherapy [80].

This intriguing phenomenon introduces novel prospects for customizing treatment approaches based on individual microbiota profiles. Nevertheless, the microbiota's involvement stretches beyond treatment efficacy. Researchers suggest that the microbiota could contribute to the development of treatment resistance, a significant challenge in oncology. Mechanisms such as drug metabolism and efflux, driven by specific microbial strains, might inadvertently lead to lower concentrations of active chemotherapy drugs reaching their intended targets [3]. Understanding the mechanisms underlying

microbiota-driven resistance is essential for devising strategies to surmount this obstacle and enhance treatment outcomes. Furthermore, the microbiota has been linked to the occurrence of adverse effects associated with chemotherapy. Effects like gastrointestinal toxicity, immunosuppression, and drug-induced dysbiosis can impact patients' well-being and treatment tolerance [6]. The delicate equilibrium between the microbiota and the host's response to chemotherapy can sway the balance toward either exacerbating or alleviating these effects. In addition, recent research into the co-metabolism of gut microbes indicates notable variation within bacterial species in their ability to metabolize drugs. This variability might account for the substantial differences in interactions between drugs and the microbiome observed among individuals undergoing treatment [43].

In the future, strategies aimed at influencing the microbiota, such as incorporating prebiotics or probiotics and novel techniques like fecal microbiota transplantation, hold promise in improving chemotherapy effects through harnessing microbial interplay. However, the implementation of these tactics in real-world medical settings demands a comprehensive assessment of their safety, effectiveness, and lasting consequences [81, 82].

In conclusion, the interdependent relationship between human microbiota and chemotherapy has become a fascinating subject of investigation with extensive implications. Exploring the ways in which microbiota influences the effectiveness of treatment and negative consequences of chemotherapy introduces fresh possibilities for improving treatment approaches and enhancing the well-being of patients. As this research progresses, it could potentially revolutionize cancer treatment by incorporating knowledge about the interaction between microbiota and chemotherapy into practice (Table 1).

Microbiota and immunotherapy

In recent times, the dynamic interplay between the microbiota within the human body and the innovative approach of immunotherapy has captured significant attention within the oncology field. The microbiota, comprising vast numbers of microorganisms inhabiting the human body, has emerged as a critical influencer of immune responses and treatment outcomes in the realm of cancer immunotherapy [87].

Immunotherapy, a revolutionary treatment strategy that capitalizes on the body's immune system to target and eliminate cancerous cells, has brought about transformative shifts in cancer treatment paradigms. Nevertheless, the responses to immunotherapy exhibit substantial variation among patients, prompting researchers to delve into factors that impact treatment effectiveness [48]. The microbiota's intricate role in governing immune function and systemic inflammation has surfaced as a potential determinant of the success of immunotherapy [49].

Studies have revealed that the makeup and variety of the gut microbiota influence how the body reacts to immune checkpoint inhibitors (ICIs), a type of immunotherapy drugs that block immune cells' inhibitory pathways to enhance the body's defenses against tumors [50]. Specific communities of microorganisms residing within the gut have been associated with favorable reactions to ICIs, whereas disruptions or imbalances in the microbiota have been connected to decreased treatment efficacy. This newfound comprehension has paved

Table 1 The effects of gut microbiota on different methods in cancer treatment

Bacteria	Therapy	Cancer type	Major findings	References
Chemotherapy				
Gammaproteobacteria	Gemcitabine	Colon cancer mouse model	Gemcitabine resistance was induced by intratumor Gammaproteobacteria, dependent on bacterial CDDL expression	[83]
Barnesiella intestinihominis	Cyclophosphamide(CP)	Cancer lesions	The gram-negative Barnesiella intestinihominis was found to improve interferon-c–producing T cell infiltration in cancer lesions to enhance the antitumor effects of CP	[84]
Immunotherapy				
Bacteroides thetaiotaomicron and Bacteroides fragilis	Anti-CTLA-4	Mouse sarcoma, melanoma, colon	Th1 induction, DC maturation (IL-12 production)	[85]
Radiotherapy				
Lactobacillus rhamnosus GG (LGG)	Radiation	Mouse model	LGG reduces radiation-induced intestinal epithelial injury and improve crypt survival	[86]

the way for innovative therapeutic strategies, including the modulation of the microbiota, to heighten the effectiveness of immunotherapy [51, 88, 89].

The mechanisms underpinning the microbiota's influence on immunotherapy are intricate and manifold. Microbial byproducts, such as short-chain fatty acids and bile acids, have the capability to regulate the functioning of immune cells and systemic inflammation. Additionally, the microbiota contributes to the training of immune cells and the fostering of a diverse array of T-cells, an essential component for launching potent antitumor immune responses. Notably, a clear connection exists between the gut microbiota and the effectiveness and potential adverse effects of ICI treatment [3, 90–92]. As a method to enhance cancer immunotherapy, one approach involves blocking immune checkpoints such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), which hinder the activity of T-cells. Ipilimumab is a monoclonal antibody designed to target CTLA-4 and is currently employed in clinical settings for treating conditions like melanoma, renal cell carcinoma, hepatocellular carcinoma, non–small cell lung cancer, and colorectal cancer. The interesting and predictable thing is that the interaction between the immune system and the gut microbiota is closely related to the effectiveness of ipilimumab (anti-CTLA-4) [93, 94].

Furthermore, emerging evidence hints at the microbiota's potential to impact the side effects tied to immunotherapy, commonly referred to as immune-related adverse events (irAEs). Recognizing the role of the microbiota in both therapeutic response and irAEs holds the potential for refining treatment outcomes and the overall well-being of patients [95]. However, translating these insights into practical clinical applications necessitates the addressing of challenges like variances in microbial composition among individuals, the intricate interactions between the microbiota and the immune system, and the possible long-term repercussions of altering the microbiota. Continuous research endeavors are concentrated on unraveling the complexities of the relationship between microbiota and immunotherapy, as well as crafting tailored interventions that can improve cancer immunotherapy's effectiveness and safety [96].

In summation, the burgeoning domain of microbiota-immunotherapy interactions has revealed an entirely new layer of intricacy within the realm of cancer treatment. The role of the microbiota in molding immune responses and treatment outcomes has introduced exciting avenues for personalized therapeutic approaches. As research advances, harnessing the potential of the microbiota has the potential to revolutionize the landscape of cancer immunotherapy, leading to elevated patient outcomes and treatments that are more finely attuned.

Microbiota and radiotherapy

The landscape of cancer treatment has traditionally been anchored in direct methods such as radiotherapy, deploying radiation to target and eliminate malignant cells. However, a paradigm shift is underway, revealing a multifaceted interplay between the intricate human microbiota—the vast community of microorganisms inhabiting our bodies—and the efficacy of radiotherapy [97]. This analysis delves into the intricate mechanisms that underscore this interrelation, casting light on its potential implications for the realm of cancer therapy. Recent revelations underscore the influential part played by the composition of the microbiota in regulating systemic immune responses and the responsiveness to radiation treatment [98]. Particularly, the gut microbiome has become known for a focal point of investigation, holding sway over immune cell populations. Fresh insights indicate that precise microbial strains, encompassing Bifidobacterium and Lactobacillus species, possess the capacity to magnify the impact of radiotherapy. These microorganisms functionally stimulate anti-tumor immune responses and mitigate tissue inflammation, potentially converging with the effects of radiation therapy [99, 100]. The immune system can be enhanced by bacteria such as *Bifidobacterium* and *Lactobacillus*. These microorganisms stimulate immune cells like dendritic cells, macrophages, and NK cells. Cancer cells are identified and destroyed by these immune cells. These probiotics can also activate T-cells, especially cytotoxic T-cells, which play an important role in maintaining antitumor immunity [101–105].

Furthermore, *Bifidobacterium* and *Lactobacillus* protect against inflammation. They reduce pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which are often elevated in cancer and can worsen tissue damage. Radiation therapy works by increasing tumor cell susceptibility through the influence of these bacteria on the tumor microenvironment. Enhanced sensitivity enhances radiotherapy's effectiveness, allowing it to be delivered at lower doses, resulting in less side effects [106, 107]. Microbe-associated molecular patterns (MAMPs) are molecular patterns that are recognized by host pattern recognition receptors (PRRs) in the intricate intercommunication between the microbiota and the host. This intricate exchange substantially shapes immune responses and molds the environment surrounding the tumor. Consequently, the constitution of the microbiota potentially governs the outcomes of radiotherapy by affecting the activation of immune cells and interactions between the immune system and tumors [97, 98]. The promise of interventions rooted in the microbiota

has galvanized research efforts aimed at optimizing radiotherapy outcomes. Clinical studies looking on the simultaneous administration of targeted probiotics or prebiotics with radiotherapy are currently underway. In addition, the notion of fecal microbiota transplantation (FMT) has gained traction as a strategy for modulating the microbiota to elicit therapeutic benefits. These strategies strive to harness the microbiota's influence on immune modulation to precisely tailor responses to radiation [108]. While the potential of microbiota-based interventions is enthralling, hurdles abound. The diversity in microbiota composition among individuals introduces variability in response to interventions. Ensuring the safety and effectiveness of interventions like FMT demands careful consideration. Thorough clinical validation remains a cornerstone before these pioneering concepts can be integrated into mainstream cancer treatment protocols [98].

The progressive illumination of microbiota-radiotherapy interactions adds layers of complexity to our understanding of the intricate interplay between our microbial inhabitants and the outcomes of cancer treatment. This revelation disrupts the conventional perspective of radiotherapy's singular effects, propelling innovative therapeutic strategies to the forefront. By harnessing the microbiota's intricate role in shaping immune responses and radiation effects, we find ourselves standing at the brink of a new era in oncology, where tailored approaches may redefine the contours of cancer treatment.

Conclusions and future perspectives

In spite of the positive clinical outcomes achieved through various anti-cancer treatment approaches, the diversity in response and the development of resistance to both chemotherapy and immunotherapy continue to be prominent challenges in cancer therapy. Recent findings have illuminated a connection between microbiota and the resistance to chemotherapy. As a result, merging anti-cancer treatments with interventions that modulate the microbiome (such as antibiotics, probiotics, and dietary adjustments) could offer innovative avenues for tackling cancers associated with microbial imbalances. This review has some limitations including the complexity of interactions between the microbiota and drugs, and the variability between individuals in the composition of their microbiomes. In future studies, standardizing microbiome analysis techniques will enable us to better understand how microbiota affect treatment resistance as well as developing personalized microbiome-targeted therapies for gastrointestinal cancer.

Abbreviations

GIC	Gastrointestinal cancer
GI	Gastrointestinal
GC	Gastric cancer
CRC	Colorectal cancer
EOCRC	Early-onset colorectal cancer
LOCRC	Late-onset CRC
DNA	Deoxyribonucleic acid
MALT	Mucosa-associated lymphoid tissue
TME	Tumor microenvironment
NICE	National Institute for Health and Care Excellence
RCT	Randomized controlled trials
PDT	Photodynamic therapy
CFU	Colony-forming units
MOD	Mode of delivery
HGF	Hepatocyte growth factor
PLCγ	Phospholipase Cγ
MAPKs	Mitogen-activated protein kinases
MMP-10	Matrix metalloproteinase-10
IL	Interleukin
ERK	Extracellular signal-regulated kinase
Th	T helper
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
GIN	Gastrointestinal intraepithelial neoplasia
NOCs	N-nitroso compounds
BFT	Bacteroides fragilis toxin
PGE	Prostaglandin E
MDSC	Myeloid derived suppresser cells
PDAC	Pancreatic ductal adenocarcinoma
ICIs	Immune checkpoint inhibitors
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
PD-1	Programmed cell death protein 1
irAEs	Immune-related Adverse events
MAMPs	Microbe-associated molecular patterns
PRRs	Pattern recognition receptors
FMT	Fecal microbiota transplantation
CP	Cyclophosphamide
LGG	Lactobacillus rhamnosus GG

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