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Review Article

The Human Microbiome: An Overview of Microbial Mechanisms, Diagnostics, and Therapeutic Modulation in Cancer

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Abstract

The human microbiome consists of trillions of microbes (microorganisms) residing in various locations in the body, but primarily in the gut. It plays a vital role in health maintenance and influences several diseases, including cancer. Emerging evidence suggests that microbial dysbiosis, characterized by an imbalance in microbial numbers and diversity, may contribute to cancer development through several mechanisms, including the release of genotoxins, altered metabolism, immune system modulation, and chronic inflammation. This narrative review compiles existing insights into the interactions between the microbiome and cancer, with a particular emphasis on microbial mechanisms during carcinogenesis and the contributions of the microbiome to the diagnosis and treatment of cancer. We examine the potential use of prebiotics, probiotics, fecal microbiota transplants, and microbial therapies that may influence cancer and its response to treatment. Gaining a deeper understanding of the intricate relationship between microbial communities and cancer could lead to groundbreaking methods for cancer prevention and therapy.

***Keywords*:** Cancer, Carcinogenesis, Human microbiome, Microbiota.

المايكروبايوم البشري نظرة عامة على الآليات المايكروبية والتشخيص والتعديل العلاجي في السرطان

الخلاصة

يتكون المايكروبايوم البشري من تريليونات الكائنات الحية الدقيقة الي تعيش في مواقع مختلفة من الجسم، وخاصة في الأمعاء. ويلعب دورًا حيوياً في الحفاظ على الصحة، ويؤثر على العديد من الأمراض، بما في ذلك السرطان. وتشير الأدلة الناشئة إلى ان خلل التوازن المايكروبي، الذي يتميز باختلال التوازن في اعداد المايكروبات وتنوعها، قد يساهم في تطور السرطان من خلال آليات متعددة، بما في ذلك إطلاق السموم الجينية، واضطرابات التمثيل الغذائي، وتعديل الجهاز المناعي، والالتهاب المزمن. تجمع هذه المراجعة الرؤية المتاحة حول التفاعلات بين المايكروبايوم والسرطان، مع التركيز على الابحاث المهمة التي تربط بين المجموعات المايكروبية وأنواع مختلفة من السرطان. وتتناول الاستخدام المحتمل للمايكروبايوم في تشخيص وعلاج السرطان.، بما في ذلك زرع مايكروبات البراز والعلاجات المايكروبية التي قد تؤثر على السرطان واستجابته للعلاج. ان فهم العلاقة المعقدة بين المجتمعات المايكروبية والسرطان قد يؤدي إلى أساليب رائدة للوقاية من السرطان وعلاجه.

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INTRODUCTION

Of the estimated 10^{12} different microbial species on earth, the human body is colonized by a relatively small number of approximately $3x10^3$ species, including bacteria, viruses, archaea, and unicellular/multicellular eukaryotes, collectively known as "microbiota" [1,2]. In line with scientific rigor and clarity, the term "microbiota" refers to the collection of microorganisms, while the microbiome encompasses not only the microorganisms but also their genomes and metabolites. Bacteria are as numerous as human body cells, and both are estimated to be around 38 trillion ($3.8x10^{13}$) [3]. The gene count of the human-colonizing microbes exceeds our genome by about 10-fold, enabling diverse metabolic functions and effects on the host, making a human being a 'hybrid organism' [4]. These microbes colonize every part of our body surface in contact with the environment, such as the gut, respiratory tract, urogenital tract, skin, etc., from birth and persist until death (Figure 1). Most of the bacteria inhabiting our body (97% of them) are in the colon, and the remainder are extracolonic. Intratumoral bacteria may also be present at an estimated average number of 0.68%, with a wide range from individual tumors exhibiting no bacteria while others contain nearly 70% bacteria by cell count [5].

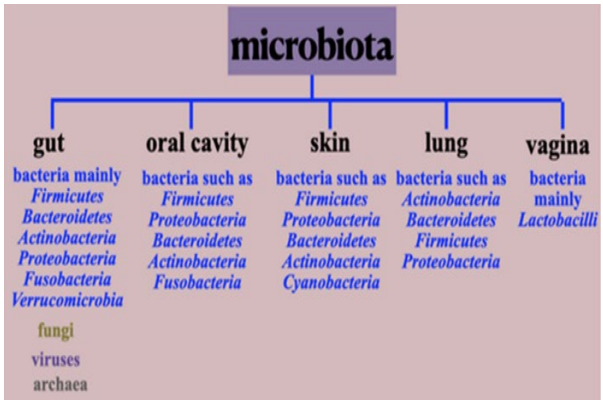

Figure 1: A general outline of the human microbiota and the habitat of its main constituents.

Both human-infecting viruses and bacteriophages may even be present in greater numbers than bacteria [6]. The focus in this narrative review will be "the bacteriome." The most microbially populated part of the human body is the gut, with the colon making up around 70% of that population [4]. The estimated surface area of the gut is about 200 m^2, which is equivalent to the area of a tennis court enriched with the required nutrients for the microbes. The bacterial content of the gut increases on travelling from the stomach to the colon, with the stomach being inhospitable to the survival of many species, containing 10 bacterial cells/g, the duodenum (10^3), the jejunum (10^4), the ileum (10^7), and the colon (10^{12}) [7]. Accordingly, the gut represents a major part of the body inhabited by microbes in numbers, varieties, and influences. Although the microbes that inhabit our body establish a beneficial relationship, it is also clear that an imbalance between the types and numbers of the microorganisms can develop. This imbalance, termed dysbiosis, can lead to diseases including cancer (Figure 2) [8]. This review aims to highlight the contribution of microbiomes to carcinogenesis and the influence it might exert on cancer treatments.

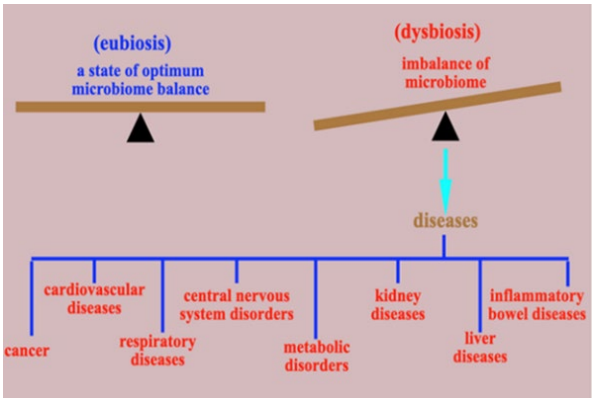

Figure 2: Imbalance of the microbiota in the body can shift the balance from the normal state of eubiosis to a diseased state of dysbiosis.

Location and Composition of the Human Microbiota

Of the large number of species of microorganisms that inhabit our bodies, only 11 of them are recognized to be carcinogenic by the International Agency for Research on Cancer (IARC) [9,10]. The list includes 7 viruses, 3 flatworms, and only one bacterium, with the conspicuous absence of members of the mycobiome (species of fungi). The human virome (the entire population of viruses in a person) is composed of 98% bacteriophages (viruses that are associated with and infect bacteria) and 2% eukaryotic viruses [11]. The seven carcinogenic viruses listed in group 1 of the IARC classification include Epstein-Barr virus (EBV, causing Burkitt lymphoma), hepatitis B virus (HBV, causing hepatocellular carcinoma), hepatitis C virus (HCV, causing hepatocellular carcinoma), Kaposi sarcoma herpesvirus (KSV, causing Kaposi sarcoma), human immunodeficiency virus-1 (HIV, causing Kaposi sarcoma and non-Hodgkin lymphoma), human papillomavirus (HPV, causing cervical cancer), and human T-cell lymphotropic virus type 1 (HTLV, causing T-cell malignancies). One additional virus associated with Merkel cell carcinoma (Merkel cell virus –MCV) is listed in group 2A of the IARC list as probably carcinogenic. The three carcinogenic flatworms on the IARC's list are *Opisthorchis viverrini* (associated with cancer of the gallbladder and its ducts), *Clonorchis sinensis* (associated with bile duct cancer), and *Schistosoma haematobium* (associated with cancer of the urinary bladder). The only bacterial species on the IARC's list is *Helicobacter pylori* (associated with stomach cancer). However, more recent studies suggest that several other bacteria could modulate or contribute to carcinogenesis, including *Fusobacterium nucleatum*, *Escherichia coli, Bacteroides fragilis,* and *Salmonella enterica* [1]. The usual habitat of microbiota, the range of microorganisms inhabiting the body, is the mucosal lining of the gut, skin, oral cavity, respiratory tract, and urogenital tract (see Figure 1). However, in addition to the mucosal microbial niche, intratumoural microbes form a distinct ecosystem that may have an impact on carcinogenesis, and their functions are only beginning to be explored [1,12]. The intratumoral microbiome promotes the progression of tumors by inducing genomic instability and mutations that can lead to alterations in the epigenome, immune/inflammatory response, and the activation of invasion and metastasis. The gut microbiota is considered the most important for health, with significant variations among individuals comparable to fingerprints [4,13]. Gut bacteria have several functions, including the stimulation of the immune response, vitamin production, fermentation of food, and the protection against pathogens [13]. The composition of the microbiota in a newborn infant resembles that of the vagina if the mode of delivery was through cesarean section and matures after three years [8]. Following that, the composition remains stable throughout adulthood unless disease onset, antibiotic use, or change of diet alters that norm [8].

Microbial Mechanisms Driving Carcinogenesis

The mechanisms by which the microbiome can influence cancer initiation and progression in the host fall into three broad categories: a) changing cell proliferation and death, b) changing the immune system function, and c) altering the metabolism. The initiation and promotion of carcinogenesis are largely dependent on the type and species of the cohabiting microbe, in addition to its interaction with the host microenvironment. Oncogenic viruses can start and spread cancer by encoding proteins that control gene expression, cell growth, cell death, and blood vessel formation, as well as immune and inflammatory responses [14]. The mycobiome, the fungal component of the microbiome, can influence carcinogenesis in several ways, including genome instability, inflammation, immunosuppression, and generally through interactions with bacterial residents [15]. The parasitic members of the microbiome may also induce carcinogenesis through the secretion of substances that

can lead to malignant transformation and/or trigger chronic inflammatory response and immune function alterations [16]. Despite the importance of the virome and the mycobiome, we will restrict our discussion to the detailed mechanisms of the bacterial content of the microbiome. Bacteria can promote cancer development and drug resistance through well-documented mechanisms that are generally classified into seven broad categories: 1) increasing genomic damage, 2) impairing DNA repairs, 3) manipulating signalling pathways, 4) altering host metabolism, 5) influencing host immunity, 6) increasing inflammation, and 7) increasing resistance to therapies [17]. There may well be substantial interconnections between these mechanisms in cancer development. Figure 3 illustrates the mechanisms by which the bacteria residing in the gut can contribute to the development of cancer and response to therapies.

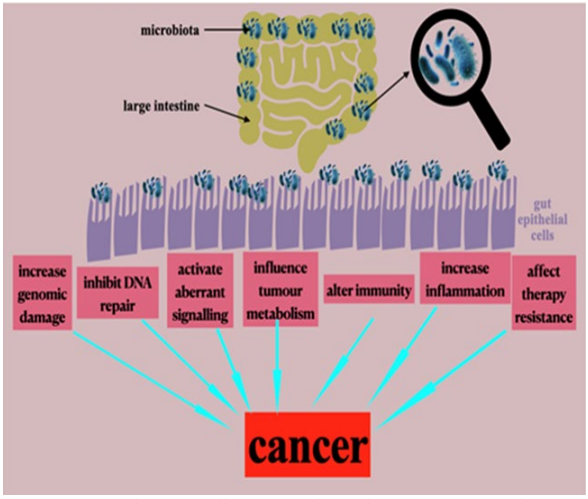

Figure 3: Mechanisms illustrating the influence of the gut bacteria in driving carcinogenesis.

Increasing genomic damage

Direct interactions of bacterial structural components and their secondary metabolites can cause host DNA mutation [18]. *H. pylori,* which colonizes the gastric mucosa of half of the world's population, can cause chronic gastric inflammation, which can progress to gastric cancer in about 1-3% of the colonized individuals [8]. The mechanism is largely attributed to the release of cytotoxin-associated gene (CagA) and the secretion of virulence factors such as VacA, urease, and NapA2 to cause host DNA damage and promote chronic inflammation and oxidative stress [19,20]. Chronic inflammation caused by the infection can also promote host genomic DNA damage, as illustrated by the fact that mice chronically infected with *H. pylori* show a 4-fold rise in mutation frequency compared to uninfected mice [21]. The polyketide synthase, *pks*, pathogenic island, which is carried by certain pathogenic strains of *E. coli,* encodes the genotoxin colibactin. Colibactin creates a crosslink between DNA strands by alkylating the DNA molecule on adenine residues. This causes double-strand breaks, which stops the cell cycle, causes senescence, and encourages the growth of cancer [17,22]. This bacterium, *E. coli*, along with several other bacterial species such as *Campylobacter jejuni,* possesses another family of enotoxins called cytolethal distending toxins (CDTs) that cause extensive DNA damage [17,20].

Impairing DNA repair

Cells frequently use DNA mismatch repair (MMR), a significant and well-studied process, to repair genes and preserve the genome. *E. coli* and *H. pylori* deplete these specialized proteins, such as MSH2 and MLH1, in cultured colon cells, thus facilitating mutagenesis [23]. The bacterium *F. nucleatum* provides a different mechanism to deplete the MMR proteins in that it increases the expression of miR-205-5p, which suppresses MSH2, MLH1, and MSH6 regulation, leading to DNA damage and cell proliferation in head and neck squamous cancer [24]. Deficient MMR activity results in a hypermutated phenotype characterized by microsatellite instability (MSI), which is prevalent in around 15% of colorectal cancers.

Manipulating signaling pathways

The cytotoxin-associated gene (CagA), already mentioned above, produced by *H. pylori* can activate β-catenin, leading to the upregulation of genes associated with gastric cancer. E-cadherin/β-catenin signaling is also turned up by substances made by other bacteria, like S. typhimurium and F. nucleatum, which are known as AvrR and FadA, respectively [25]. The AvrR protein is also inserted into host cells during *Salmonella* infections to activate JAK/STAT and β-catenin/Wnt signaling, ultimately leading to cancer [26]. *Salmonella typhimurium* infection particularly activates MAPK/Akt signaling, which is essential in the maintenance of gallbladder cancer in mouse models of this disease [27]. The binding of FadA, secreted by *F. nucleatum*, to E-cadherin inhibits this protein's tumor suppressor activity [8]. *Porphyromonas gingivalis* promotes cell proliferation in colorectal cancer through the activation of the MAPK/ERK signalling pathway [28]. Dysregulation of tumor suppressor proteins such as p53, PTEN, and pRb by certain microbes can induce STAT3 signaling, leading to enhanced epithelial-mesenchymal transition and senescence [17].

Altering host metabolism

Bacteria can regulate the glycolysis of the immune cells through toll-like receptor (TLR) signaling. When TLR was activated in macrophages, for instance, the glycolysis was significantly raised, thus increasing the expression of the glucose transporter, GLUT1, and the enzymes hexokinase and enolase [29]. The increased TLR signaling also induces a metabolic shift from oxidative phosphorylation to glycolysis. Bacteria such as *Bacteroides uniformis* have a strong capacity for glycolysis and the production of butyrate, which accumulates in cancer cells due to the Warburg Effect, acting as inhibitors of histone deacetylation [30]. The inhibition of histone deacetylation induces apoptosis and suppresses cell proliferation in colorectal cancer [31]. About 95% of the bile acids that are released into the intestine are reabsorbed through the portal vein and

return to the liver to be recycled. This hepatic-intestinal cycle takes place several times a day (roughly about 6 times a day in humans) [17]. Bile acids can serve as signalling molecules through binding to receptors such as the farnesoid X receptor (FXR), predominantly found in the nucleus of liver and ileum cells. These receptors play a role in the production, transportation, and usage of triglycerides and the metabolism of other lipid molecules [32].

Influencing host immunity

Bacteria and the molecules associated with them activate and recruit innate cells such as NK cells, neutrophils, macrophages, myeloid-derived suppressor cells, and innate lymphoid cells. Additionally, cells from the adaptive immune system, including T and B cells, influence changes in the immune system [33]. The killing ability of NK cells is directly inhibited by the presence of *F. nucleatum* in the TME [34]. This inhibition is partly mediated by the binding of the bacterial Fap2 protein to the human TIGIT receptor. Moreover, increased presence of *F. nucleatum* in the colorectal tumor microenvironment is associated with a reduced number of $CD3^+$T cells, which are known to have favorable clinical outcomes [35]. Fap2 is overexpressed in inflamed colon and particularly enriched in colonic adenomas (benign) and adenocarcinoma (malignant) tissues, where it can exist bound to the carbohydrate molecules Gal-GalNac (a disaccharide often used as a tumour marker) [36]. Bacteria can also influence response to immunotherapy, as in the case of several commensals such as *Bifidobacterium longum*, *Collinsella aerofaciens,* and *Enterococcus faecium,* which were found to yield better outcomes to anti-PD1 therapy when present [34]. *Helicobacter pylori* bacteria activate TLR2 and TLR4, causing profound effects on the host immune response through the secretion of inflammatory cytokines such as IL-1β and IL-18 [37].

Increasing inflammation

Mouse models of carcinogenesis generally revealed that the gut epithelium with a higher density of polyps has a higher permeability compared to healthy tissues, thus allowing more transmucosal bacterial translocation [38]. These translocated bacteria then induce the release of pro-inflammatory cytokines such as IL-6, IL-11, IL-17, IL-22, and IL-23, which participate in cancer progression [20,38]. Short-chain fatty acids (SCFAs), particularly butyrate and propionate, can downregulate the expression of pro-inflammatory cytokines [39]. It is thought that *H. pylori* affects the growth of cancer mainly through inflammatory pathways that are controlled by neutrophils and lymphocytes and boosted by cytokines like IL-1β, TNFα, and IFNγ [9]. FadA secreted by *F. nucleatum* binds to epithelial and endothelial cells, allowing cellular internalization and the induction of pro-inflammatory cytokines like IL-6 and NF-κB that can result in oral squamous cell carcinoma [40]. Enterotoxigenic *B. fragilis* is associated with colitis and colon cancer through its secreted toxin, BFT [41]. This toxin stimulates inflammation in colorectal cancer by targeting the tight junctions of cells in the intestine, cleaving E-cadherin, and increasing permeability and inflammation [9].

Increasing resistance to therapy

Resistance to cancer therapy can arise from interactions between the microbiota and the intended therapy, influencing drug metabolism and/or host immunity. The microbiota, and their derivatives, can break down medicines and directly convert them into nontoxic metabolites (or with reduced toxicity) [42]. For example, the bacteria *Mycoplasma hyorhinis* have many enzymes, such as thymidine phosphatase, which break down pyrimidine nucleoside analogues, a class of drugs resembling the building blocks of DNA or RNA that are used to treat cancer and various infections [43]. The same bacteria also possess cytidine deaminase and pyrimidine nucleoside phosphorylase, which can reduce the toxicity (in this case, a desired biological effect) of the chemotherapy drug gemcitabine. Bacteria can also mediate host tolerance to chemotherapies. For instance, irinotecan (a topoisomerase 1 inhibitor employed for several cancers) is converted to the metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) by the intestinal bacteria. The active metabolite, SN-38, is then inactivated by glucuronidation to its inactive form, SN-38G [44]. Certain species of *Clostridium* convert the inactive form, SN-38G, back again to the active SN-38, resulting in severe diarrhea [17]. Ionizing radiation, when used as anticancer therapy, is partially mediated by the stimulation of the major arms of the immune system, innate and adaptive immunity. The main reason for tolerance against this form of therapy is attributed to the disruption of the gut bacteria [17]. Gram-positive bacteria reduce the activity of dendritic cells and other antigen-presenting cells, limit $CD8^+$T cell activity, and weaken radiation-induced antitumor response. Vancomycin was shown to improve the radiation-mediated anticancer effect by eliminating gram-positive bacteria [45]. Not all bacteria have a negative influence on cancer therapies. It was found that vitamin B6 produced by *E. coli* is needed for fluorouracil efficacy to be realized in the model organism *C. elegans* [46]. Certain species of *Enterococcus* might elevate intratumoral $CD8^+$/Treg cell ratio, thus permitting a more immunosupportive environment.

Contributions of the Microbiome to the Diagnosis and Therapy of Cancer

The microbiota inhabiting our bodies could influence the diagnosis and management of cancer in three ways: 1) in diagnosis, 2) in modulating the effects of other cancer treatment modalities, and 3) in driving new treatment options (Figure 4).

The Microbiome in the Diagnosis of Cancer

The main criteria for a good diagnostic method for the detection of cancer are being sensitive, specific, non-invasive, and able to discover malignancy early enough

to institute preventative and/or treatment measures. Three main options for sampling are available: 1) through the saliva, 2) through the fecal material, and 3) through the plasma for DNA.

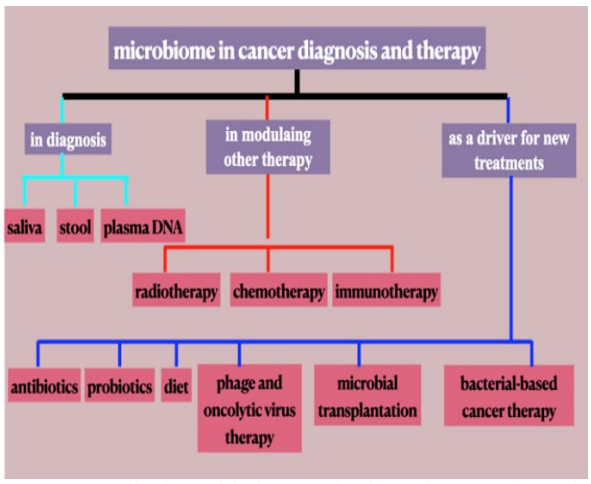

Figure 4: Applications of the human microbiome in cancer diagnosis and therapy.

Through salivary sampling

A combination of three bacteria, *Capnocytophaga gingivalis*, *Prevotella melaninogenica,* and *Streptococcus mitis,* was found to be a good diagnostic indicator in patients with oral squamous cell carcinoma (OSCC) compared to controls, with specificity and sensitivity more than 80% [47]. Saliva samples with *Neisseria elongata* and *Streptococcus mitis* yielded a specificity of 82% and a sensitivity of 96% in patients with pancreatic cancer [48]. In patients with squamous cell lung cancer, a combination of two bacterial genera, *Capnocytophaga* and *Veillonella*, served as a diagnostic indicator with 87% specificity and 85% sensitivity compared with controls [49]. The salivary microbiome sampling is non-invasive and easy to collect, but a lack of collection standards may be one of its main drawbacks.

Through fecal (stool) sampling

Here, most of the supporting research focused on colorectal cancer. A stool sample having a combination of *Lachnoclostridium* species with *F. nucleatum*, *Hungatella hathewayi,* and *Bacteroides clarns* yielded a specificity of 81% and a sensitivity of 94% [50]. Accuracy and consistency across populations remain challenges that require further investigation.

Through Plasma DNA (liquid biopsy)

The microbes might leave DNA fragments indicating their presence in different tissues. Circulating pieces of these DNAs in the plasma could act as a useful diagnostic indicator. A next-generation sequencing analysis revealed that these DNA fragments relate to bacteria, though some were also from fungi and viruses [51]. Chen and colleagues developed a model for the early diagnosis of lung cancer and for the prediction of disease recurrence after surgery based on circulating microbial DNA [52]. This diagnostic test yielded a sensitivity of 87.7% and achieved an area under the curve (a measure of the overall accuracy in distinguishing between diseased and healthy individuals) of 93.2%. Moreover, this test demonstrated the capability to detect early lung cancer with a sensitivity of more than 86%. Although plasma DNA analysis can be a cost-effective diagnostic tool for lung cancer, the method requires further investigation to be applied across many cancers.

The microbiome in modulating cancer therapies

The microbiome was found to be associated with the effects of different forms of cancer therapies, including 1) radiotherapy, 2) chemotherapy, and 3) immunotherapy.

Radiotherapy

The gut microbiome can influence how patients respond to radiotherapy, affecting both its effectiveness and side effects. Eradication of Gram-positive bacteria using antibiotics improved the antitumor effects of radiation in melanoma, cervical cancer, and lung cancer in mouse models of these diseases [45,53]. Also, the reintroduction of sodium butyrate, a metabolite of SCFAs normally produced by Gram-positive bacteria, nullified the improvement in radiotherapy seen with antibiotic treatment [45]. The complete removal of all the gut bacteria has been shown to reduce the efficacy of radiation treatment in breast cancer and melanoma models, while the complete eradication of all the fungi improved this efficacy, possibly due to the opposing effects on immune recruitment [54].

Chemotherapy

Published evidence suggests that the gut microbiome is associated with the outcomes of chemotherapy treatment and its side effects [55]. The purpose of chemotherapy is to disrupt cell division, which triggers apoptosis and, occasionally, an immune response. Some normal cells, which are also subject to cell division, can also be affected, leading to the commonly observed side effects of these therapies. *Fusobacterium nucleatum*, for example, can activate autophagy, promote chemoresistance, and inhibit the caspase pathway [56]. Reducing the gut microbiota by antibiotics has led to reduced effects of chemotherapy drugs such as cisplatin and oxaliplatin in colon cancers and lymphomas [57]. Fecal microbiota transfer (FMT) to mice revealed that *Paraprevotella clara* is associated with responders to the action of oxaliplatin, while *B. fragilis* was linked with non-responders [58]. When focusing on individual metabolites, it was found that indole-3-acetic acid can increase the therapeutic efficacy of FOLFIRINOX (a mix of chemicals containing folinic acid, fluorouracil, irinotecan, and oxaliplatin) in patients with pancreatic ductal adenocarcinoma [59]. Bacteria within the tumor can also influence chemotherapeutic efficacy, as illustrated by the human commensal *E. coli*. These bacteria were found to increase the toxicity of tegafur and mercaptopurine while lowering that of doxorubicin and

mitoxantrone through their influence on the metabolism of these chemotherapeutic agents [60].

Immunotherapy

The gut microbiome can influence the patient's immune response and manipulate the effectiveness of anticancer medicines [61,62]. The three main immune checkpoint therapies targeted by drugs are CTLA-4, PD-1, and PD-L1 [63]. Drugs targeting CTLA-4 were found to be most effective in the presence of the gut microbiome. Recolonization with *B. fragilis*, *Bacteroides thetaiotaomicron,* and *Burkholderia cepacia* (or their recombination) following antibiotic treatment has led to improved anti-CTLA-4 efficacy [64]. Ablation of the gut microbiome with antibiotics has been shown to reduce tumor growth in mouse models of pancreatic ductal adenocarcinoma, particularly when combined with anti-PD-1 immunotherapies [65]. As PD-L1 represents the ligand expressed by tumour cells for the receptor PD-1, which is expressed by T cells, both proteins have been shown to be similarly dependent on the gut microbiome. The use of CAR-T cells is another arm of immunotherapy, and studies have shown that patients receiving broad-spectrum antibiotics were more likely to have worse survival outcomes [66].

The Microbiome Driving New Cancer Treatments

Microbiota-driven cancer therapies have the potential to improve cancer outcomes. These types of treatments are considered briefly in the following sections.

Antibiotics

Antibiotics can alter the microbiota and their metabolism, thus modulating the immune response [17]. The quinolone group of antibiotics eliminates the pathogenic bacteria *Klebsiella pneumoniae* and improves the survival rate of pancreatic cancer patients [67]. Also, mice nebulized with vancomycin/neomycin caused a reduction in the bacterial load of the lungs associated with a reduction in Treg cells and an activation of T and NK cells, leading to a significant decrease in lung metastasis [68]. More recently, CRISPR-Cas-based antimicrobials emerged to eliminate detrimental bacteria while preserving the beneficial microbiome. However, system delivery and safety in avoiding unintended genetic changes remain significant challenges. Additionally, studies have shown that antibiotics may also promote carcinogenesis by promoting chronic inflammation, leading to genotoxicity and weakened immune response, thereby adversely impacting cancer treatment and acting as a double-edged sword [69].

Probiotics

Probiotics are live microorganisms that have been explored for their potential to manipulate the gut microbiome and improve cancer treatment outcomes. Probiotics can enhance the efficacy of cancer therapies, reduce side effects, and potentially prevent cancer development by modulating the gut's microbial environment [70]. This treatment mainly consists of *Lactobacillus* and *Bifidobacterium* species [17]. Probiotics influence carcinogenesis by regulating gut bacteria and their metabolism and inhibiting the production of carcinogenic substances [71]. They can also inhibit immune response and apoptosis, which ultimately affects cancer progression.

Diet

The food we consume plays a crucial role in shaping our microbiome, generating metabolites that can modulate carcinogenesis and cancer treatment response [72]. The non-digestible part of the diet, prebiotics, can affect the content and function of the microbiome, resulting in beneficial effects in enhancing the effectiveness of cancer therapies, particularly immunotherapies [73]. Examples of prebiotics include the different types of oligosaccharides, inulin, and resistant starch, which are preferentially metabolized by different bacteria into SCFAs, mainly acetate, propionate, and butyrate. Prebiotics can improve resistance against pathogenic bacteria, maintain the integrity of the mucous and colonic epithelial cells, and improve anticancer effects [74,75]. A diet high in processed foods and low in fiber may negatively influence the microbiome and reduce treatment efficacy [76].

Bacteriophage and oncolytic virus therapy

While antibiotics can control bacterial growth, they possess a dysbiotic action on the microbiome and often fail to penetrate biofilms [77]. Bacteriophages (viruses that infect bacteria) and other oncolytic viruses can be used for the treatment of cancer, the former for their ability to attack and eliminate unwanted bacteria, and the latter for killing cancer cells. Bacteriophages can target intratumoral bacteria and cause lysis of these microorganisms to help reduce tumor growth. Bacteriophages can target and eliminate *F. nucleatum*, a bacterium implicated in colorectal cancer, and enhance the activity and effectiveness of chemotherapy [78]. Other viruses might be employed for their ability to target and eliminate cancer cells, as in the case of Talimogene laherparepvec (T-VEC). This product is a genetically engineered herpes simplex virus type 1 that replicates in tumor cells to induce an antitumor response in melanoma [79,80].

Microbial transplantation

Fecal microbial transplantation (FMT) and selective microbial transplantation (SMT) are becoming potential therapies in cancer treatment, particularly in conjunction with immunotherapy [81]. It involves transferring gut bacteria from a healthy donor to a patient to restore/alter the microbial balance of the host and potentially improve the body's immune response to cancer. Microbial transplantation, through regulating the host's immune response, may improve the performance of cancer therapies such as immune checkpoint inhibitors [82]. Several clinical trials are currently taking place investigating the effect of FMT on a variety of cancer types.

Bacterial-based cancer therapy

A few bacteria can naturally target and accumulate in tumours and can be used to deliver therapeutic agents to the cancer cells or stimulate the immune response to eliminate them. Some bacteria can induce immune responses, through the activation of T cells and cytokines, which recognize and eliminate cancer cells [83,84]. *E. coli* was shown to activate T lymphocytes to attack tumour cells, and *Salmonella typhimurium* was found to activate cytokines such as IL-1β, TNF-α IL-18 [84]. Other bacteria release substances, proteins, or toxins, such as colicin from *E. coli* and microcin E492 from *Klebsiella pneumoniae,* to infiltrate and destroy the cancer cell [85,86]. *Streptococci* bacteria have been proven to clear tumors by releasing polysaccharides, forming a biofilm that represses the attachment of cancer cells to endothelial cells [84]. Additionally, bacteria can serve as carriers to deliver cancer medicine to tumors. Bacteria of the genus *Salmonella* have been shown to express a protein called endostatin, which can block angiogenesis [87].

Conclusions

A large and growing body of research has shown the profound effect of the human microbiome on cancer development, progression, and treatment response. Accumulating evidence revealed that the gut microbiome, in addition to intratumoral bacteria, modulates the immune function and metabolic processes. Dysbiosis, a state of imbalance of the body's microbial community, has been associated with various cancers, pointing to its diagnostic and therapeutic applications. Challenges remain, including the need for better and standardized methodologies for the assessment of the commensal microbial community and any changes that may occur following cancer and its treatment. The microbiome's main value likely lies in its role as a modifying factor influencing risk, progression, and response to cancer therapies. Considering that, future research could note interindividual variations in the microbiome and design personalized microbiome interventions, paving the way for innovative "standalone" therapy or therapy in conjunction with other more established approaches.

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Conflict of interests

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Data sharing statement

N/A.

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