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The Role of Microbiome in Cancer Cell Stimulation and Therapy

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

In recent times, the microbiome has been increasingly recognized as having a hand in various disease states that include cancer as a part. Our commensal and symbiotic microbiota, in addition to pathogens with oncogenesis features, have tumor-suppressive characteristics. Our nutrition and other environmental influences can modulate some microbial species representatives within our digestive system and other systems. The microbiota has recently shown a two-way link to cancer immunotherapy for both the prognosis and the therapeutic aspects. Preclinical results indicated that microbiota modification could be transformed into a novel technique to improve cancer therapy's effectiveness. This article aimed to review recent development in our understanding of the microbiome and its relationship to cancer cells and discuss how the microbiome stimulates cancer and its clinical and therapeutic applications. Such information was selected and extracted from the PubMed, Web of Science, and Google Scholar databases for published data from 2000 to 2020 using relevant keywords containing a combination of terms, including the microbiome, cancer, immune response, immune response, and microbiota. Finally, we concluded that studying the human microbiome is necessary because it provides a thorough understanding of humans' interaction and their indigenous microbiota. The microbiome provides useful insight into future research studies to optimize these species to fight life-threatening diseases such as cancer and has rendered the microbiome a successful cancer treatment strategy.

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1. INTRODUCTION

Trillions of different microbes, collectively known as the microbiome, live in humans. The terms microbiome and microbiota often refer to each other interchangeably: the former refers to the genomes of all microorganisms in the organism, the latter refers to the microorganisms in the body. The microbiota also includes viruses, fungi, protozoa and archaea, and bacteria [1], [2]. Even so, there are variations in microbiome composition between species and within the same species, which are primarily due to host genetics and environmental influences, as well as their interactions with one another [3,4].

Cancer remains one of the major causes of death and morbidity world-wide, resulting from the growth of malignant cells into tumor-related masses, leading to DNA mutations that contribute to genetic variations in tumor progression and carcinogenesis with many diseases [5]. In various ways, microbes play a major role in human health and disease, including the development of cancer. Cancer cells and microbes coexist in our body's systems, and both need resources to exist and develop. What we eat, particularly if we have more nutrients than energy, will support cancer cells and microbial cells [6], [7]. Consequently, factors impact the proliferation and survival of cancer cells and microbes. These results suggest that cancer cell-microbe cell interactions play a vital role in cancer stimulation and progression [8], [9].

Studies show that Bacteria can play a role in carcinogenesis in various ways, including bacterial- derived carcinogens, and dysbiosis and part of the immune response, which is inflammation resulting from bacterial infection [10,11]. Previous studies have shown that *Helicobacter pylori* have been closely linked to gastric cancer development as a result of bacterial secretion of carcinogens [12]. Fusobacterium nucleatum has been shown to increase epithelial cell proliferation and the infiltration into the colon, with increased activation of β-catenin, both of which result in increased tumor and inflammatory responses [13]. Various *Escherichia coli (E. coil)* are associated with inflammation and can alter the microbiota structure, which can contribute to tumor production [14].

Aside from carcinogenic effects, there is evidence that the microbiome can help or hinder chemotherapies and immunotherapies' effectiveness. Even in clinical trials, the destruction of the commensal microbiota by broad-spectrum antibiotics has been shown to negatively affect cancer immunotherapy outcomes, illustrating the role of the commensal microbiota in controlling immune response for cancer therapy [10,15].

This article aims to review recent development in our understanding of the microbiome and its relationship to cancer cells and discuss how the microbiome stimulates cancer and its clinical and therapeutic applications.

2. THE HUMAN MICROBIOME

2.1 An Overview of the Human Microbiome

The current study is a modern result of many classical microbiology advancements, including genomics and microbiology, which has given classical microbiology a new perspective. Their goal was thusly focused on the microbiomes, which are the Human Microbiome Project's main targets (HMP) [16]. Once researchers had characterized the microbial living in the human body, they shifted their focus to the microbes that live in the human body and the role they take concerning health and disease. The importance due to the release of the first human genome has risen substantially [17].

We have 10^{14} microbial cells in our bodies that are believed to be 10-fold greater than our somatic and germ cells combined. They are made up of bacteria, archaea, viruses, and eukaryotes [18,19]. The microbiota harbor 100-fold more genes than the human genome [20]. Most bacteria, viruses, and fungi are found on the epithelium of the skin, nares, the respiratory system [21-23], the ductal systems of both exocrine and endocrine organs such as the vagina, the breast and the digestive system [24-26]. Some bacteria leave the Gastrointestinal (GI) tract and join the blood circulation. There is evidence that a small number may accumulate in tumors because of tumor vasculature allowing residence and extravasation [27].

Humans, like most other species, receive large quantities of microbiota from their mothers during birth. Although there are many smaller improvements to be made during childhood, adolescence is the prime of life, followed by increased complexity and immobility in middle age and later complexity, or simply, adulthood [28,29].

The introduction of 16S ribosomal RNA hypervariable sequencing and shotgun sequencing approaches to characterize microbes at different body sites has shown in the last decade that their diversity and abundance are culturable in an independent manner [18,20].

The human microbiome is in flux in response to factors influencing the host. Determinants such as age, diet, hormones, or disease influence the human microbiome at each stage of existence alterations in the human (dysbiosis) can cause life-threatening illness sufficient evidence shows that a well-balanced microbiota is relevant to overall health [30].

Changes in lifestyle and social expectations affect the microbiome at any point in life. The newborn baby's microbiota is dramatically varied by the delivery method: Vaginal versus cesarean delivery and breast than formula feeding [31]. The microbiota of the elderly is affected by lifestyle far later in life, with people residing in long-term residential care facilities exhibiting less variability than people living separately in the community [32]. Animal studies indicate that infants and children are highly susceptible to low-dose antibiotics in the food supply, resulting in obesity through microbiological changes [33].

2.2 Distribution and Disease of the Human Microbiome

Of all the human systemic microbiomes, the gut microbiome, which is made up of the microorganisms' genetic material in the gut, holds a very significant and specific role. They are important in various physiological processes such as metabolism, immunity production, and nutrient supply. The host's genotype and immune system have been shown to influence gut microbiota production [34]. The bacteria within our body influences the health of our overall well- being. However, there is an alteration in the gut microbiota known as dysbiosis that may induce vulnerability to pathology. Balancing its dysfunction can cause multiple diseases such as inflammatory bowel disease, kidney disease, high blood pressure, cardiovascular disease, obesity, atherosclerosis, allergy, and numerous other illnesses [35].

The gut microbiota is involved in the development of both acute attack and chronic inflammatory bowel disease, according to the research of Sunil and his colleagues. The epithelium is an effective physical barrier that limits substances' movement through the epithelial layer [36]. If the intestine is injured, the cell adhesion barrier can be disturbed [37]. The airways and lungs were excluded from the Human Microbiome Project [6] (HMP) study at its inception, as these sections were thought to be sterile. This was always appropriate due to the unfavorable outcomes of the numerous standard microbiological culture experiments performed on healthy individuals [38].

The authors published the first application of culture-independent techniques to classify microbiota present in the lungs of healthy patients and patients with asthma and chronic obstructive pulmonary disease in a landmark study in 2010 [39]. Modern methods have produced over 30 studies documenting the bacterial diversity in the lower respiratory tracts of healthy individuals [40]. The intestinal and immune system axis plays an essential part in the functioning of the central nervous system [41]. Moreover, the gut microbiota impacts the hypothalamic-hypophysis-adrenal axis and therefore plays its part in the responses to stress [42].

Researchers using molecular techniques have stated that the disease-free arteries and veins are microbe-free in nature [43]. Some people's blood vessels were found to be free of bacteria and viruses. Various microorganisms, such as the pathogenic microbes *Helicobacter pylori, cytomegalovirus, Chlamydia pneumoniae,* and *herpes virus,* as well as the *virus Mycoplasma*, were found in the healthy aortic artery as well as the internal mammary arteries [44]. Li et al conducted a clinical trial on two populations: those at low risk of cardiovascular disease and those with cardiovascular disease risk. In their study, an intestinal flora imbalance was discovered to be related to cardiovascular disease [45]. Lower intestinal perfusion and intestinal barrier disturbance had been noted as a couple of reduced cardiac output causes. Increased systemic inflammation contributes to endotoxemia, which in turn promotes endothelial cell death, making the heart even more

vulnerable to endotoxin-induced complications [46]. Until recently, many believed that the human urinary tract and urine were sterile, but modern science has shown otherwise. after an examination of the urine, the most frequently found genera are *Streptococcus* and *Lactobacillus* (for women and men, respectively), which can do a protective role [47]. However, a clinical study in 2015 revealed a link between gut microbiota and chronic kidney disease. The investigators detected translocation of the microbiota in individuals undergoing hemodialysis [48]. The findings showed that an alteration in the intestinal microbiota could result in a synthesis of nitrogen compounds that affect the tight junction's integrity, which enables the transfer of their toxins to other parts of the body and triggers kidney diseases.

3. THE MICROBIOME AND ITS RELATIONSHIP WITH CANCER STIMULATION

3.1 Microbial Pathogens Cause Cancers

Cancer is one of the most prevalent diseases, representing the second leading cause of death worldwide [49] with approximately 19.3 million new cases and 10 million cancer-related deaths estimated in 2020 [50]. Microbes are believed to be involved in about 10–20% of human cancers. One microbe has been called a carcinogen by the International Agency for carcinogenesis, which is the bacterium *Helicobacter pylori* for its association with stomach cancer [51]. The disturbance of the human microbiome is associated with various cancers, including gastric, colorectal, pancreatic, and breast cancer, as shown in Table 1[52]. At the time of the award of the Nobel Prize for Physiology in 2005, Dr. Marshall found that *Helicobacter pylori* are an etiologic agent of stomach ulcers. [53].

Recent microbiome research suggests that commensals and opportunistic pathogens may also be cancer-related infections and may be more frequent than the current estimate of 15–20 percent. Colorectal tumors, for example, have higher levels of *Fusobacterium nucleatum* than normal colonic tissue. Previously, this bacterium was related to periodontitis and appendicitis but not cancer [54], [55].

Environmental and host factors affect breast cancer progression directly in the case of breast cancer. However, also induces breast cancer in bacterial cultures. Bacillus, members of the *Enterobacteriaceae* and *Staphylococcus*, are more likely to occur in individuals with breast cancer than healthy people. In addition, it has led to a double-stranded breach in HeLa DNA from patients with cancer, isolated Escherichia coli and Staphylococcus epidermidis. Lactobacillus spp. was not present in the breast tissue of people with breast cancer who contribute to various health benefits [56].

Bacteroides massiliensis has been linked to an increase in the prevalence of prostate cancer. The dynamic associations between cancer and the human microbiota have been aided by a change in the human microbiota [57].

Table 1. Microbial pathogens cause Cancers

Microbe	Cancer	Reference
Helicobacter pylori	Gastric adenocarcinoma	[58]
Streptococcus	Oesophageal cancer	[59-61]
Prevotella and Veillonella		
Fusobacterium nucleatum, Enterobacteriaceae, Methanobrevibacter	Colorectal tubular adenoma, adenocarcinoma	[62,63]
Selenomonas and Leptotrichia species	Colorectal cancer	[64,65]
Enterobacteriaceae, Pseudomonadaceae, Moraxellaceae and Enterococcaceae	Pancreatic cancer	[66]
Alistipes Sphingomonas and Methyl bacterium		[67,68]
Enterobacteriaceae and Staphylococcus	Breast cancer	[59]
Propiono bacterium Acnes		[69,70,71,57]
Bacteroides massiliensis	Prostate cancer	
Fusobacterium, Prevotella and Gemella species	Head and neck cancer	[72]
Mycobacterium tuberculosis	Lung cancer	[73]

3.2 Microbiome and Cancer Stimulation

Studies are infancy on the involvement of microbiota in cancer, but data indicate that microbiota can affect carcinogenesis and cancer treatment responses. Cancer cells can also build a microenvironment around the tumor that promotes their development This environment promotes tumor growth factors, angiogenesis, and fibroblasts [74,75]. The microenvironment is essential in tumor growth but sometimes hinders it. If immune regulation has not occurred, the microenvironment may help to suppress cancer [76]

Moreover, there were different mechanisms by which microbes promote carcinogenesis, as shown in Fig. 1 and Table 2.

Microbes injectors inject host cells. These effectors modulate the signaling of Wnt/b-catenin by b- catenin [78]. As a result of a Barrier Breakdown, pro-inflammatory signaling causes genomic instability and chronic inflammation [79], [80]. Several human viruses, including human papillomaviruses (HPV), hepatitis B (HBV) and C viruses (HCV), human T-cell leukemia virus-1 (HTLV) being involved in T-cell leukemia, Epstein–Barr virus (EBV), and Kaposi sarcoma- associated herpesvirus (KSHV), are known to cause various cancers. They have been shown to convert nonpermissive cell types and show evidence of tumorigenesis in animal models. During the early stages of infection and the viruses alter epigenetic programs and DNA repair mechanisms differently. Carcinogenesis is facilitated by these distortions of the host genome [79,81].

Dysbiosis and alteration of the microbiome host relations can induce carcinogenesis through increased bacterial translocation and immune dysregulation. Microorganisms secrete molecules that are detected by toll-like receptors (TLRs) in several cell types. TLR4, the receptor for lipopolysaccharides (LPS), present in both gram-negative cell walled bacteria and liver and pancreatic cells, is implicated in the liver and pancreatic cancer. Major signaling pathways for tumor-derived nuclear factor kappa (NF) and STAT3 have been shown to be essential in oncogenic [82].

Microorganisms may change the tumor microenvironment by influencing cancer cells. Furthermore, several strains of *E. coli* can be found in the rectum of people with colorectal cancer as well as in healthy individuals [83]. Colibactin generates growth factors in the surrounding cells, stimulating tumor growth [84]. One way microbes can affect the microenvironment is by creating bacterial biofilms which are known to increase the number of cells and risk of colorectal cancer [85].

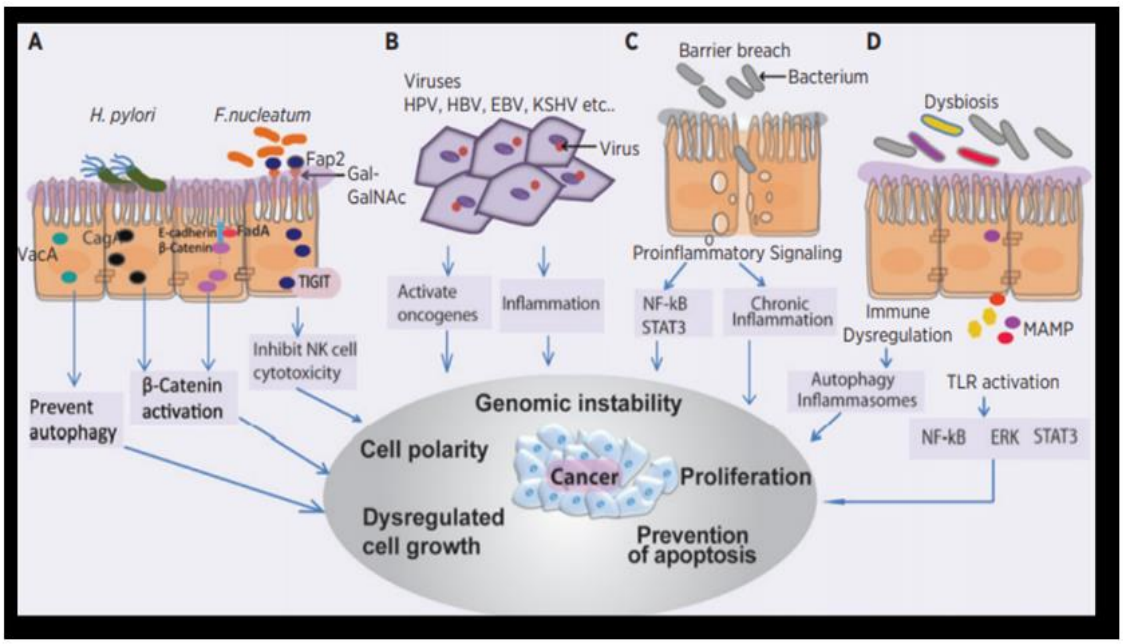

Fig. 1. Mechanisms to facilitate carcinogenesis by microbes [77]

Table 2. Mechanisms by which microbes promote carcinogenesis

Mechanisms promote carcinogenesis	Microbe	Cancer	Mechanism	Reference
Loss of epithelial barrier	Fusobacterium nucleatum	Colorectal cancer	modulating E-cadherin/b-catenin signaling.	[13]
	Escherichia coli	colitis-associated colorectal cancer	Bacterial toxins, such as colibactin allows bacterial access to intestinal epithelium	[14]
Activation of inflammation	Gram-negative bacterial	hepatocarcinogenesis	Sustained accumulation of lipopolysaccharide (LPS)	[88]
	Clostridium species	Liver cancer	Induction of IL-1β and IL-6	[89]
Genotoxic effect	Escherichia coli	colitis-associated colorectal cancer	Producing calobactin that induces double- strand breaks	[14]
	Helicobacter	gastric adenocarcinoma	Reactive oxygen specious production	[90]
Attempting to avoid immune damage	Helicobacter	gastric adenocarcinoma	Induction of Tregs T-cell proliferation and prevention of Epithelial PD-L1	[90]
	Fusobacterium nucleatum	Colorectal cancer	The Fap2 proteins, interact with T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and inhibit the natural killer cell- mediated immunosurveillance of cancer	[91]
Metabolic effect	Bacteroides and Firmicutes	Colorectal cancer	Released short chain fatty acids, such as butyrate, acetate, and propionate.	[92,93]

Approximately half of *Helicobacter pylori*-induced gastric cancer is thought to be related to chronic gastric inflammation, oxidative stress, and DNA damage that may play a role in carcinogenesis [86], [87]. The pathogen translocated CagA to gastric epithelial cells, which significantly modifies b-catenin to improve stomach cancer chances [78].

4. IMPACT OF THE MICROBIOME ON IMMUNITY

The immune system is composed of a complex network of innate and adaptive components endowed with an extraordinary capacity to adapt and respond to highly diverse challenges. The microbiota plays a fundamental role in the host immune system's induction, training, and function [94].

4.1 Impact on Innate Immune Response

A key characteristic of the cells presenting in intestinal antigen (APCs) is its ability to defend the body from infection while retaining immune tolerance to normal gut microbiota. Dendritic cells (DCs) of Peyer's patches produce high levels of interleukin-10 (IL-10), compared with splenic DCs activated under similar conditions [95]. Gut macrophages are located near the intestinal microbiota, and they have a peculiar "immunologic nature, a phenotype called "inflammation aversion," consequently [96]. Microbe-assigned microbial stimulants such as TLR ligands, several molecular patterns associated with microbes, do not generate pro-inflammatory cytokines [97].

Neutrophils are an innate defense part of the immune system and have been shown to have a systemic effect on the rest of the microbe population. Heat-killed *E. coli* strain, autoclaved cecal material, or LPS can rescue neutrophil reductions in microbiota-depleted models [98]. Fig. 2 depicts the neutrophil response to microbiota. To prevent inflammatory responses against the epithelium and commensals, the microbiota induces a regulatory network that suppresses neutrophil recruitment. Segmented filamentous bacteria (SFB) and other commensals may induce T helper (Th) Th17 cells, which secrete IL-17 to recruit neutrophils to the intestinal epithelium, resulting in neutrophil-mediated negative feedback control of the microbiota. Neutrophils also produce IL-22, which stimulates the development of IgA by intestinal B cells. In the mucosal system, macrophages and DCs contain a significant amount of pro-IL1. Promoted neutrophils may recruit into the intestinal lumen to create an ordered intraluminal structure that prevents commensal and pathogenic species from translocating and expanding [99].

According to traditional scientific understanding, natural killer cells are innate lymphocytes that can identify and destroy transformed and infected cells. It has recently been discovered that there are two groups of natural cytotoxins expressed by NK cells in the mucosa [100].

4.2 Impact on Adaptive Immune Response

The main component of the adaptive immune system is found in CD4+ T cells. Most CD4+ cells in the small intestine are found in the lamina propria (LP). Following stimulation, naive CD4+ T cells differentiate into four major subsets: 1) Th1, 2) Th2, 3) Th17, and 4) Treg (Treg). Transcription factors and cytokines play a key role in differentiating different CD4+ T cell subsets. The gut microbiota, both inside and outside the gut, has a key role in CD4+ T cell growth. [101].

Peyer's patches are where the dominant B cell immunoglobulin (Ig) secreting Intestinal IgA has been reported to be approximately 0.8 grams of intestine produced per day [102]. The Peyer's patches' number and cellularity were reduced, and there was a decline in IgA and plasma cells in the intestine [102]. Thus, the gut microbiota is a major driving force for mucosal IgA production; a large dose of live bacteria (10^9 colony-forming unit or CFU) was needed to induce a high titer of secretory IgA.

5. EVIDENCE LINKING THE MICROBIOME TO CANCER THERAPY

The treatment component of cancer poses the most difficulty for the medical community regarding its effectiveness and affordability. Cancer eradication is necessary and beneficial due to this disease's existence, which will affect all facets of human life, including poor quality of life, psychology, and financial toxicity. To do so, innovative treatment options for both treating and preventing cancer are needed to alleviate the major burden of cancer [103].

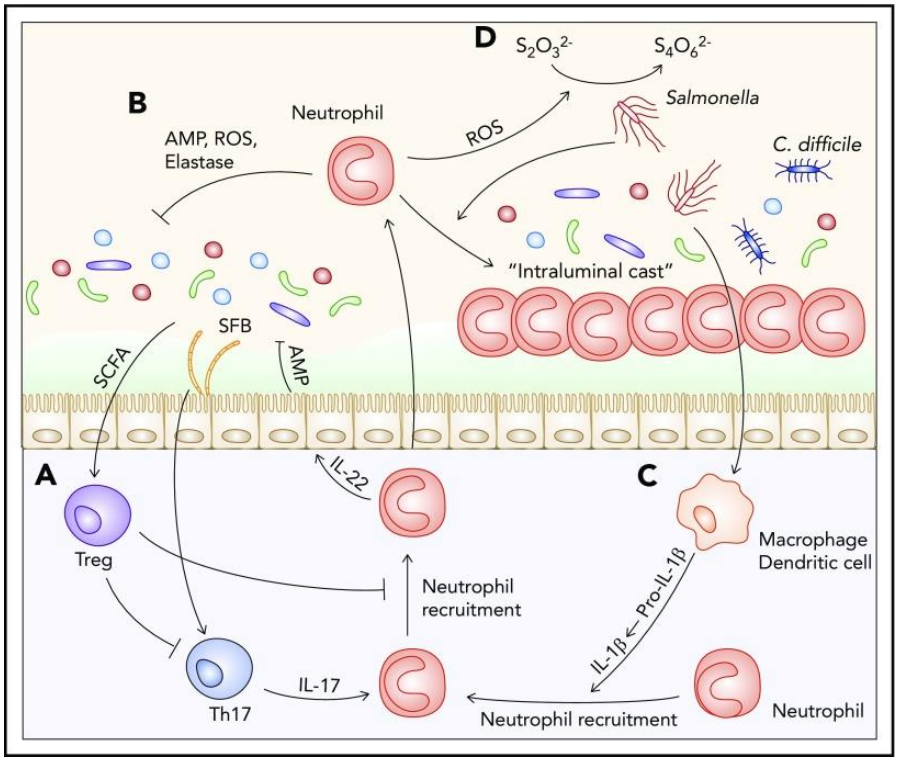

Fig. 2. Neutrophil response toward the microbiota [99]

It has recently been discovered that there is a close relationship between the human host and the microbiome, and this forgotten organ performs novel functions in human health [104].

The gut microbiome is critical for producing and controlling adaptive and innate immunity (Fig. 3). The gut microbiome serves as a buffer against bacterial invasion and infection and influences the effectiveness of hematopoietic-cell transplantation and chemotherapy [105]. As a result, it has been proposed that the gut microbiome will modulate the immune system and affect the effectiveness of immunotherapy [106], chemotherapy [107] and hematopoietic cell transplantation [108].

Compared to normal mice, the function of the gut microbiome is evident in germ-free mice that live in an environment devoid of microorganisms. Germ-free mice develop a deficient immune system, especially in the gut, with an altered mucosal layer; a decrease in the amount and function of Peyer's patches and lymphoid tissues; and a decrease in immune cell counts, microbe detecting TLR, and major histocompatibility complex II molecules for an immune response [109].

5.1 Microbiome to Improve Cancer Therapies Effectiveness

Cancer immunotherapy is an emerging treatment option for cancer patients. It makes use of the immune system to battle tumors [110]. Increasing evidence suggests that the gut microbiome plays a significant role in cancer care. They have a significant impact on the peripheral immune system [111], [112].

Immune checkpoint inhibitors (ICIs) have shown promising clinical results in advanced hematologic malignancies, as demonstrated by monoclonal antibodies (mAbs) blocking the cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) pathways [113], [114]. Recent research has shown that the gut microbiota influences the therapeutic effectiveness of ICIs against cancer [115],[16]. They discovered that patients with higher *Faecalibacterium prausnitzii* density and low Bacteroides abundance after anti-CTLA-4 therapy had a higher risk of colitis [116], [117].

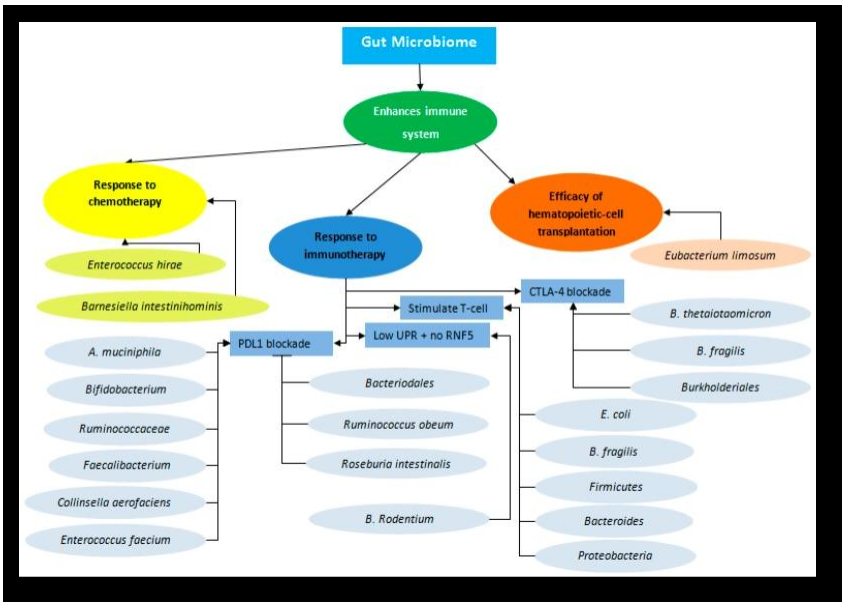

Fig. 3. Role of the gut microbiome in the innate and adaptive immune response [105]

Patients with melanoma who received anti-CTLA-4 therapy and were abundant in *Bacteroidetes* and different genetic pathways leading to polyamine transport and did not form colitis [118]. Treg differentiation can be linked to the well-known effects of these bacteria having on the immune system [119].

Pancreatic cancer also has a microbiome loaded with representatives of the Gammaproteobacteria, including *Mycoplasma hyorhinis*, which has recently been demonstrated to contain when these microbes were applied to pancreatic tumors in mice, they conferred gemcitabine tolerance. After mice were treated with the antibiotic ciprofloxacin, the antitumor effect was recovered [66].

Some (forms of) cancer treatments might be improved by bacterial vaccines. These vaccines are usually inactivated or contain only bacterial components; they have fewer adverse effects on the immune system's tumor-fighting capability. As an example, BCG contains bacteria components, including Staphylococcus and Streptococcus. These bacteria are associated with inflammation and tumor development, and preliminary research found that inactivated strains have been found to be effective as adjuvant therapy in non-small cell lung cancer patients (NSCLC) [120]. More recently, an increase in Pseudomonas aeruginosa was associated with lung cancer development and tumor progression [121]. But when a *Pseudo aeruginosa* preparation (PAP), inactivated bacteria, is administered to patients with advanced NSCLC, there is an improvement in cisplatin efficacy. P. aeruginosa has powerful immuno-stimulating properties, resulting in a better than normal response. Some PAPs are thought to be linked with regression in breast, liver, and stomach cancer as well. Bacterial vaccines can be employed as an adjuvant treatment, constantly stimulating the innate-mediated antitumor response [119].

The immunological efficacy of cyclophosphamide has also depended on the microbiome. Cyclophosphamide compromises the gut barrier through direct injury to the intestinal epithelium, mobilizing microorganisms to the gut-associated lymphoid tissue, which boosts the production of Th17 responses [107].

1970s therapy gave rise to a Mycobacterium Bovis strain BCG, which acted mainly as an immunostimulatory treatment for low-risk intravesical cancer in clinical trials. In the case of urinary bladder cancer, BCG's instillation will trigger a powerful antitumor immune response. It appears to use a wide range of immune-boosting methods to initiate the antitumor response [122]. An in a head-to-to-head clinical study, two separate Connaught strains displayed vastly different efficacies. The Connaught strain appeared to be more inflammatory and to induce a stronger Th1 immune response in mice. Even though the two strains were genetically identical and presumably originated from the same sample in the 1920s, Connaught was found to

have a greater superoxide dismutase activity than Tice, resulting in longer persistence [123].

5.2 Microbiomes affect Cancer Therapies Effectiveness

Several different species of mycoplasma impact cancer. Mycoplasma preferably colonizes tumors because it is a highly nutrient-rich tumor ecosystem in which the bacteria thrive. [124]. Mycoplasma also interacts with anticancer drugs in unique ways. Mycoplasma-infected cell lines developed resistance to antimetabolites and the p53 activator nutlin due to p53 destabilization and DNA repair protein inhibition by the Mycoplasma DnaK chaperone protein raising the likelihood of malignant transformation [125].

Multiple studies found that the therapeutic effectiveness was reduced in the absence of the gut microbiota, implying that commensal microbes modulate the anticancer immune responses induced by the rapies through various which share characteristics with Th1 and Th17 cells. The removal of the gut microbiota in germ-free or antibiotic-treated mice results in drug resistance to cyclophosphamide [107].

6. POTENTIAL FUTURE CLINICAL APPLICATIONS

6.1 Use of Antibiotics in Conjunction with Cancer Therapy

Antibiotics medications are produced in the life of microorganisms or higher organisms that have antipathogenic or other antibacterial properties and interfere with other cells' growth [126]. More scientific studies show that antibiotics can trigger cell death, slow cancer growth, and protect it from spreading. Antibiotics are often used to treat cancer for these reasons another name is anticancer antibiotics [127].

They mainly consist of peptides and anthraquinones that have a direct and powerful inhibitory action on uncontrolled cancer proliferation, uncontrolled proliferation, and metastatic spread. Anticancer antibiotics are classified primarily as anthracyclines, mitomycin, bleomycin, actinomycin, guanorycin, and enediyne. Furthermore, their anticancer effects are both complicated and efficient [128], [129].

Knowledge of cancer etiology has progressed to the cellular and molecular levels due to modern science and technology development, particularly biomedicine in the twentieth century. According to modern cell biology, cancers are a form of the cellular disease characterized by irregular cell development. Because each cancer begins with a single cell, cancer cells' malignant behavior is passed down through cell proliferation. Also, cancers are diseases that involve changes in the structure and function of genetic material. Meanwhile, cancer cells' invasive growth and metastasis also promote the incidence and progression of cancer [130].

It can be concluded from Fig. 4 that anticancer antibiotics have three mechanisms, which are anti-proliferative, pro-apoptotic, and anti-epithelial-mesenchymal-transition [131].

In terms of the molecular mechanism of anticancer antibiotics, anticancer antibiotics can destroy cells during the replication cycle, including G0 cells, achieving anti-proliferation capacity of cancer cells by affecting the cell mechanisms. Cyclophosphamide, a licensed chemotherapeutic d
cycle, as seen with cyclinenon-specific drugs [131]. On the other hand, anticancer antibiotics may promote cancer cell apoptosis by targeting apoptotic genes B cell lymphoma-2, caspase, and cancer suppressor gene P53, thereby influencing cancer cell apoptosis in patients [132]. Furthermore, anticancer antibiotics can be used to prevent cancer cell metastasis and play an anti-metastasis role. Ciprofloxacin promotes apoptosis, while valinomycin inhibits cancer proliferation [133].

Anthracycline antibiotics, including doxorubicin and daunomycin, are commonly used in the treatment of cancer in humans. Although the exact role of anthracycline's "antitumor action" is unknown, possible mechanisms include DNA intercalation, free radical formation, and DNA binding and alkylation or cross-linking [134]. Bleomycin is an antibiotic that can be incorporated in DNA with iron complexes, causing antibacterial single-strand and double-strand breaks in DNA. Bleomycin has recently been used as a successful therapeutic anticancer medication to treat germ cell tumors, lymphomas, and squamous cell carcinoma [135]. Ciprofloxacin has been shown in *vitro* to be effective in human and animal cancer cell lines, including human bladder cancer, human colorectal, hamster ovarian cancer, and human hepatocellular carcinoma cell lines. [136-137]. Furthermore, ciprofloxacin derivatives caused G2/M phase arrest through a p53/p21 dependent

pathway. Ciprofloxacin may thus have an anti-proliferative effect [138].

The clinical implementation of targeted drugs has brought positive news to patients with terminal diseases, at the very least enhancing their quality of life and extending their survival time. However, new "targeted medications" are costly and must be administered daily. And it should be taken for at least a month. Furthermore, selective treatment does not have the effect of a radical cure and is ineffective for all tumors and all patients, which is a significant drawback [130].

6.2 Use of the Microbiome as a Prognostic Biomarker

The composition of the microbiome may be used as an additional prognostic or predictive biomarker for treatment outcomes. Certain bacteria were found to be enriched in anti-PD-1 responders, while others were found to be enriched in non-responders. These results indicate that fecal DNA sequencing before therapy, quantifying population richness and the relative proportion of putatively defined "beneficial" or "detrimental" bacteria, can be predictive of outcome and eventually aid in treatment decision-making [139].

6.3 Use of the Pre / Probiotics as Cancer Therapy

The current traditional approach to cancer care consists of the use of conventional treatment. Even so, the long-term efficacy and protection of these chemotherapeutic drugs and oncologic agents have yet to be determined. Thus, these drugs destroy both cancerous and noncancerous cells [140]. Because these cytotoxic drugs often induce malignant neoplasms, there are many life-threatening side effects other than tumor regression that contribute the most to the worsening of the overall condition [141].

Probiotics are essential to combat and assist with various types of cancer. For this article's purposes, the word "probiotic" shall apply to functionality, not taxonomy. More commonly known as conventional fermented foods have these types of probiotic microbes. Natural microbes should be used. Otherwise, they are genetic engineering of some kind. A microbiological supplement is known as a 'living product' or a 'biotherapeutic live agent' when used in dietary supplements. Probiotics are used in various industries such as fruit, nutritional supplement, dietary supplement, and probiotic development [142]. Dead probiotics and their metabolites are also extremely important in tumor prevention and control [143].

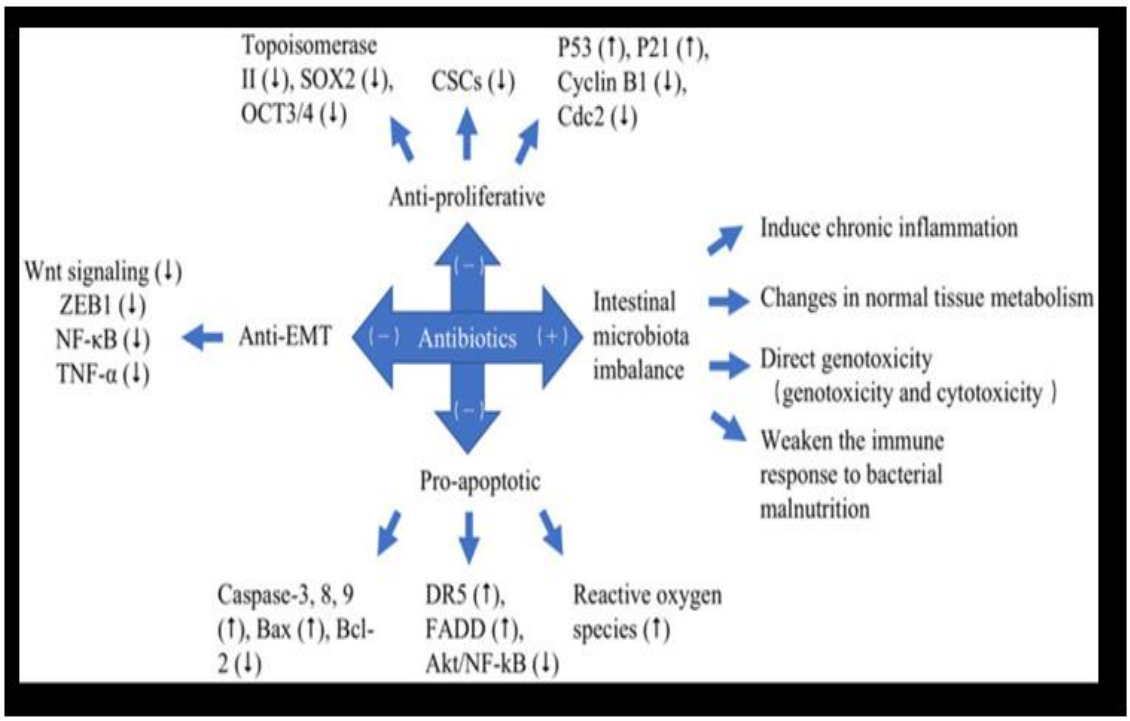

Fig. 4. The mechanisms of Anti-cancer antibiotics [130]

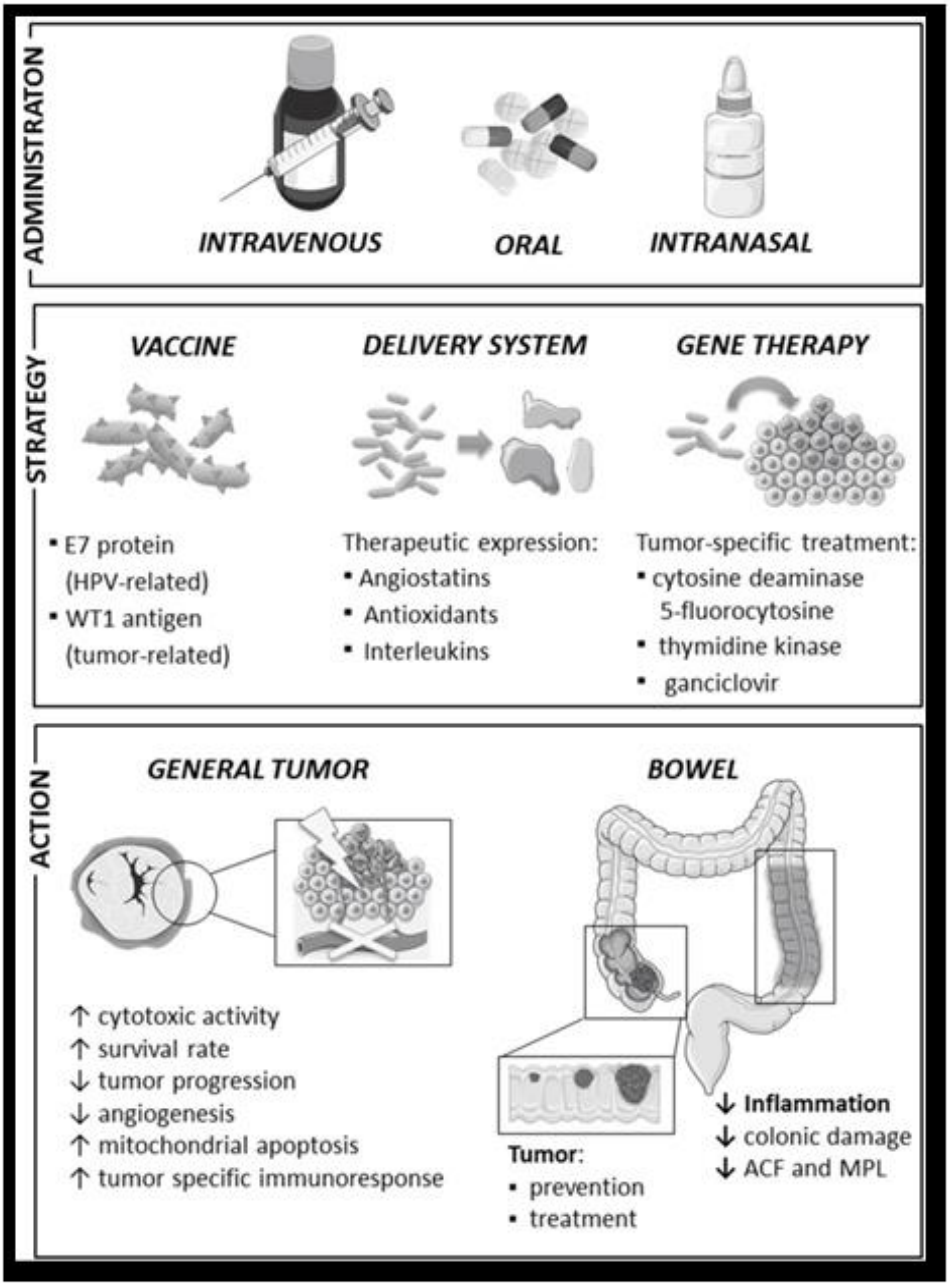

Fig. 5. Possible treatment and cancer prevention use of probiotic bacteria [147]

The main probiotic mechanisms of anticancerous and antimutagenic properties are binding, acidogenic degradation, and preventing mutagen formation from procarcinogen substances, and hosts' innate-modulation using anti-inflammatory molecules [144].

Laboratory and animal studies demonstrate that probiotics, prebiotics, and synbiotics (a mix of probiotics) effectively prevent cancer [144]. Inulin (prebiotic) is a fermentable non-digestible food additive that makes the host healthier Prebiotic fibers, like fiber, help protect against colon cancer. The mechanism of action of colorectal-cancer inhibition involves preserving the stool's bulking, binding of carcinogens to bacteria, regulation of xenobiotic-metabolizing enzymes, and immune responses in the caecum, as well as cecal immunological responses [145].

The association between a diet rich in *Lactobacillus* and a reduction in colorectal cancer

incidence was first demonstrated in Goldin and Gorbach (40 percent vs. 77 percent in controls) [146]. Because of their ability to modulate cancer cells' proliferation and apoptosis, probiotics have been studied both in vitro and in vivo. The potentiality of new therapy may be an alternative to invasive therapy, such as chemotherapy or radiation therapy [147].

Anti-tumor effects of probiotics remain uncertain in a particular mechanism. Gut microbiota has several pathways in this phase that are essential. To preserve homeostasis, probiotic bacteria play a key role and preserve sustainable physicochemical conditions in the colon. Reduced pH due, among other things, to excessive bile acids in feces can be a direct cytotoxic factor that affects the colonic epithelium leading to carcinogenesis of the colon [148].

Probiotics preserve the metabolic health of the other types of microflorae in the intestines. When *E. coli* and *Clostridium perfringens* normally found in the intestine produce carcinogenic enzymes including b-glucuronidase and azoreductase [149].

The binding and degradation of possible carcinogens may be a cancer-preventing technique that chiefly involves the bacteria *Lactobacillus* and *Bifidobacterium* strains. Many cancer cases are directly or indirectly linked to the use of carcinogens present in food, particularly fried meat. The mutagenic effects of a diet high in cooked meat were countered by a *lactobacilli* supplement taken by human volunteers, resulting in lower urinary and feces heterocyclic amines levels [150], [151].

It is only over the past decade or two that the probiotic-delivery strategy has found unexpected success for delivering different molecules, such as medicines, cytokines, or even DNA, for rectal cancer is very novel (Figure 5) [152]. The technique is simple, cost-effective, and suitable for use in the treatment of different disorders.

7. CONCLUSION

Microbiome research has emerged and encouraging pre-preliminary findings on the role of the microbiome concept in cancer care have emerged. We have come to understand the microbiome's function in cancer and immunity; however, the mechanism itself is unclear. Finding a method to increase the effectiveness of cancer immunotherapy for the gut microbiome also presents some new challenges. In a clinical trial, it is unclear which microbiome components appear to be most effective at fostering an anti-tumor immune response. An adequate understanding of these interactions will allow us to help the host's immune surveillance and increase host resistance to attack.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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