

The Role of Microbiome in Cancer Cell Stimulation and Therapy

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.

Keywords: microbiota, microbiome, probiotics, cancer, cancer stimulation, cancer therapy, immune response

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 particular 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 *H. 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. coli*) 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 [21] of the skin, nares, the respiratory system [22], [23], the ductal systems of both exocrine and endocrine organs such as the vagina [24], the breast [25]and the digestive system [26]. Much of the microbiota live in our digestive system, while archaea, viruses, and eukaryotes are also found elsewhere in our body [27], [28]. Some bacteria leave the 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 [29].

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 [30], [31].

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 [32].

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 [33]. 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 [34]. Animal studies indicate that infants and children are highly susceptible to low-dose antibiotics in the food supply, resulting in obesity through microbiological changes [35].

2.2. Distribution and Disease of the Human Microbiome

Of all of 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 [36]. 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 [37].

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 [38]. If the intestine is injured, the cell adhesion barrier can be disturbed [39]. The airways and lungs were excluded from the 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 [40], [41]. 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 [42]. Modern methods have produced over 30 studies documenting the bacterial diversity in the lower respiratory tracts of healthy individuals [43]. The intestinal and immune system axis plays an essential part in the functioning of the central nervous system [44]. Moreover, the gut microbiota impacts the hypothalamic-hypophysis-adrenal axis and therefore plays its part in the responses to stress [45].

Researchers using molecular techniques have stated that the disease-free arteries and veins are microbe-free in nature [46], [47]. 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 [48]. Recent research 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 [49], [50]. Another research reported that 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 [51]. 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 [52]. 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 [53]. 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 [54], [55], with approximately 18.1 million new cases and 9.6 million cancer-related deaths estimated in 2018 [56]. Microbes have a crucial role in human health and disease, one of which is to influence cancer risk. Microbes are currently thought to influence cancer risk by changing DNA, speeding up cell proliferation, derailing cell cycle regulation mechanisms, and facilitating the survival of aberrant cells [7]. 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 [57]. The disturbance of the human microbiome is associated with various cancers, including gastric, colorectal, pancreatic, and breast cancer, as shown in Table 1 [58]. 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. [59].

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 [60]–[62].

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 [63].

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 [64].

Table1: Microbial pathogens cause cancers:

Microbe	cancer	Reference
Helicobacter pylori	Gastric adenocarcinoma	[65]
Streptococcus	Oesophageal cancer	[66]
Prevotella and Veillonella		[67]
		[68]
Fusobacterium nucleatum, Enterobacteriaceae, Methanobrevibacter	Colorectal tubular adenoma, adenocarcinoma	[69] [70]
Selenomonas and Leptotrichia species	Colorectal cancer	[71] [72]
Enterobacteriaceae, Pseudomonadaceae, Moraxellaceae and Enterococcaceae	Pancreatic cancer	[73]
Alistipes	Breast cancer	[74]
Sphingomonas and Methyl bacterium		[75]
Enterobacteriaceae and Staphylococcus		[63]
Propiono bacterium		
Acnes	Prostate cancer	[76] [77] [78]
Bacteroides massiliensis		[64]
Fusobacterium, Prevotella and Gemella species	Head and neck cancer	[79]
Mycobacterium tuberculosis	Lung cancer	[80], [81]

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 [82], [83]. This environment promotes tumor growth factors, angiogenesis, and fibroblasts [83]. The microenvironment is essential in tumor growth but sometimes hinders it. If immune regulation has not occurred, the microenvironment may help to suppress cancer [82], [84], [85].

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

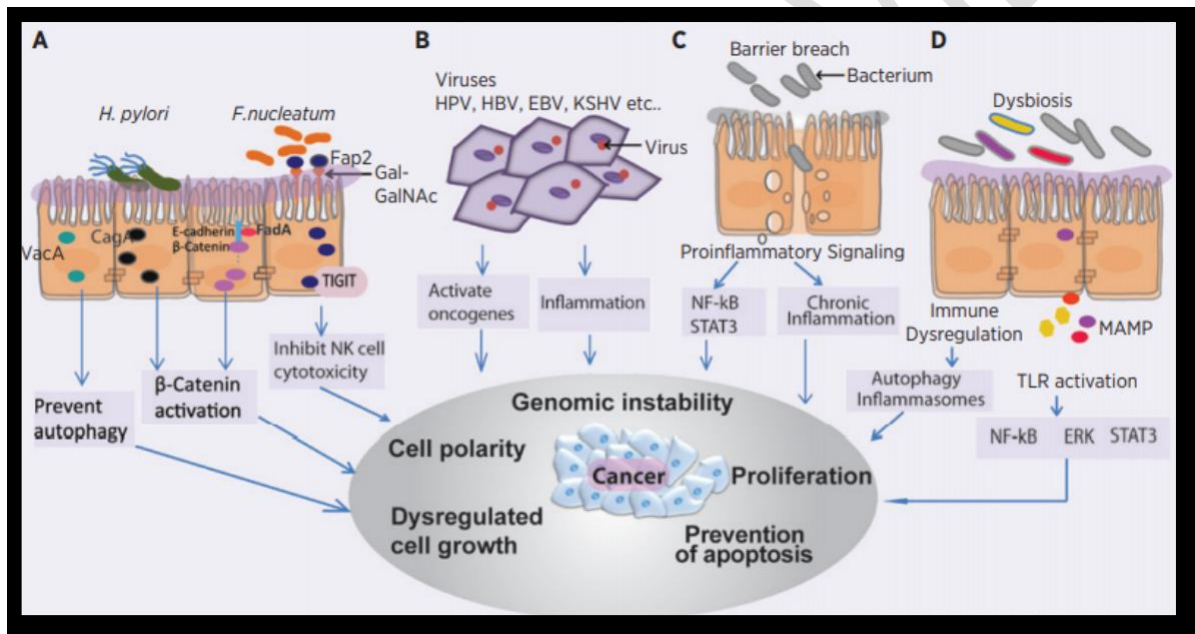


Figure 1: Mechanisms to facilitate carcinogenesis by microbes [86].

Microbes injectors inject host cells. These effectors modulate the signaling of Wnt/b-catenin by b-catenin [87]. As a result of a Barrier Breakdown, pro-inflammatory signaling causes genomic instability and chronic inflammation [88], [89]. 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 [87], [90], [91].

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 [92].

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 [93]. Colibactin generates growth factors in the surrounding cells, stimulating tumor growth [94]. 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 [95].

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 [96]–[98]. The pathogen translocated CagA to gastric epithelial cells, which significantly modifies b-catenin to improve stomach cancer chances [87].

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)	[99]
	Clostridium species	Liver cancer	Induction of IL-1 β and IL-6	[100]
Genotoxic effect	Escherichia coli	colitis-associated colorectal cancer	Producing calobactin that induces double-strand breaks	[14]
	Helicobacter	gastric adenocarcinoma	Reactive oxygen specious production	[101]
Attempting to avoid immune damage	Helicobacter	gastric adenocarcinoma	Induction of Tregs T-cell proliferation and prevention of Epithelial PD-L1	[101]
	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	[102]
Metabolic effect	Bacteroides and Firmicutes	Colorectal cancer	Released short chain fatty acids, such as butyrate, acetate, and propionate.	[103], [104]

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 [105].

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 [106]. Gut macrophages are located near the intestinal microbiota, and they have a peculiar "immunologic nature, a phenotype called "inflammation aversion," as a consequence [107]. Microbe-associated microbial stimulants such as TLR ligands, several molecular patterns associated with microbes, do not generate pro-inflammatory cytokines [108].

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 [109]. Figure 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 [110].

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 [111].

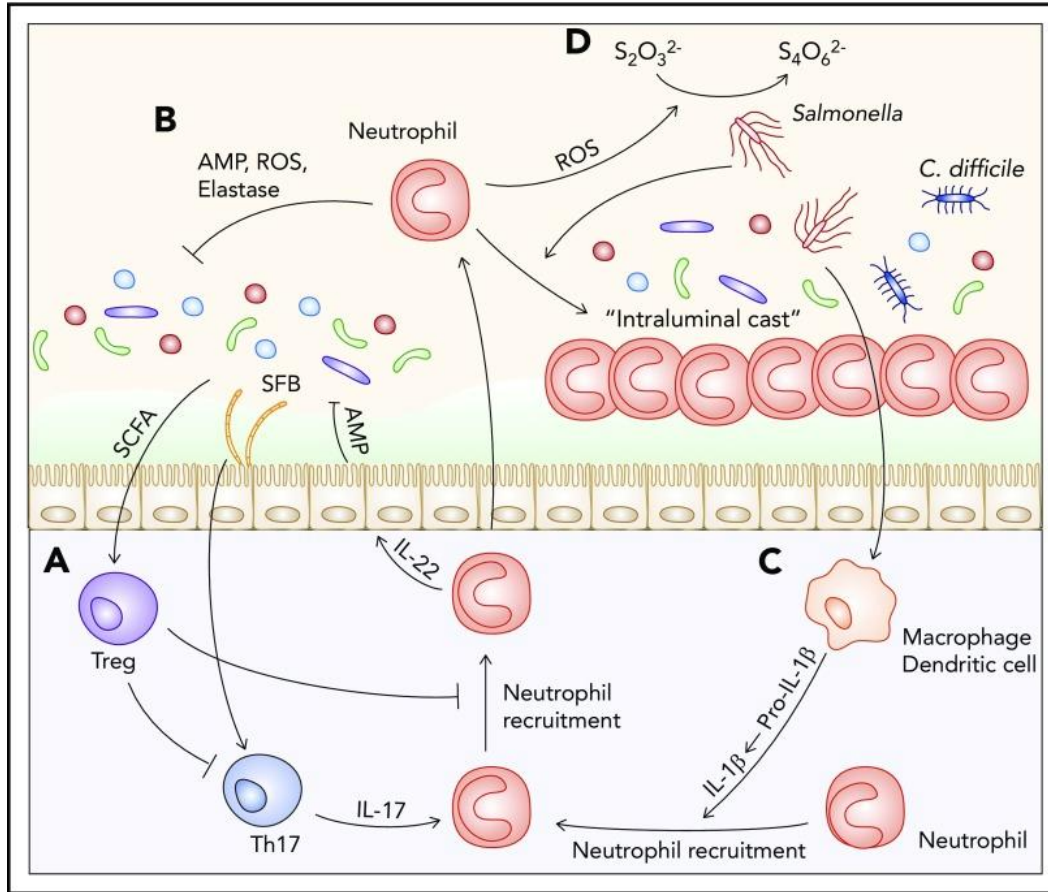


Figure 2: Neutrophil response toward the microbiota [110].

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. [112].

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 [113]. The Peyer's patches' number and cellularity were reduced, and there was a decline in IgA and plasma cells in the intestine [113]. Thus, the gut microbiota is a major driving force for mucosal IgA production; a large dose of live bacteria (10⁹ 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 actually poses the most difficulty for the medical community regarding its effectiveness and affordability. Over one investigation predicted that the total treatment-related costs of current cancer patients in the United States were \$1157.75 to \$7975 a day [114]. 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 in order to alleviate the major burden of cancer.

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 [115]. In various body sites, the microbiota has been reported to influence both the gastrointestinal tract and the entire immune system [26].

The gut microbiome is critical for producing and controlling adaptive and innate immunity (Figure 3). The gut microbiome serves as a buffer against bacterial invasion and infection and influences the effectiveness of hematopoietic-cell transplantation and chemotherapy [116]. As a result, it has been proposed that the gut microbiome will modulate the immune system and affect the effectiveness of immunotherapy[117], chemotherapy[118], and hematopoietic cell transplantation[119].

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 [120].

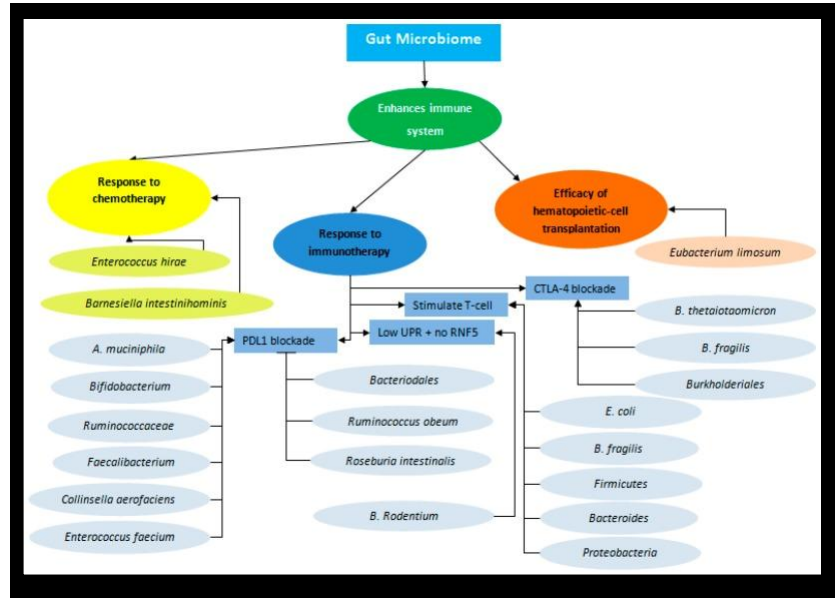


Figure 3: Role of the gut microbiome in the innate and adaptive immune response [116].

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 [121]. Increasing evidence suggests that the gut microbiome plays a significant role in cancer care. They have a significant impact on the peripheral immune system [122], [123].

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 [124], [125]. Recent research has shown that the gut microbiota influences the therapeutic effectiveness of ICIs against cancer [126]–[128]. They discovered that patients with higher *Faecalibacterium prausnitzii* density and low *Bacteroides* abundance after anti-CTLA-4 therapy had a higher risk of colitis [127], [128].

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 [129]. Treg differentiation can be linked to the well-known effects of these bacteria having on the immune system [130].

Pancreatic cancer also has a microbiome loaded with representatives of the Gammaproteobacteria, including *Mycoplasma hyorhinitis*, 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 [73].

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) [131]. More recently, an increase in *Pseudomonas aeruginosa* was associated with lung cancer development and tumor progression [132]. 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 [130].

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 [118].

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 [133]. 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 [134].

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. [135]. 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 [136].

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 therapies through various mechanisms. Cyclophosphamide, a licensed chemotherapeutic drug, has been shown to alter the intestinal microbiota composition in mice and facilitate the translocation of specific Gram-positive bacteria into secondary lymphoid organs, thereby stimulating the development of 'pathogenic' Th17 cells, 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 [118].

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 [137]. 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 [138].

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[139], [140].

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 [141].

It can be concluded from **Figure 4** that anticancer antibiotics have three mechanisms, which are anti-proliferative, pro-apoptotic, and anti-epithelial-mesenchymal-transition [141].

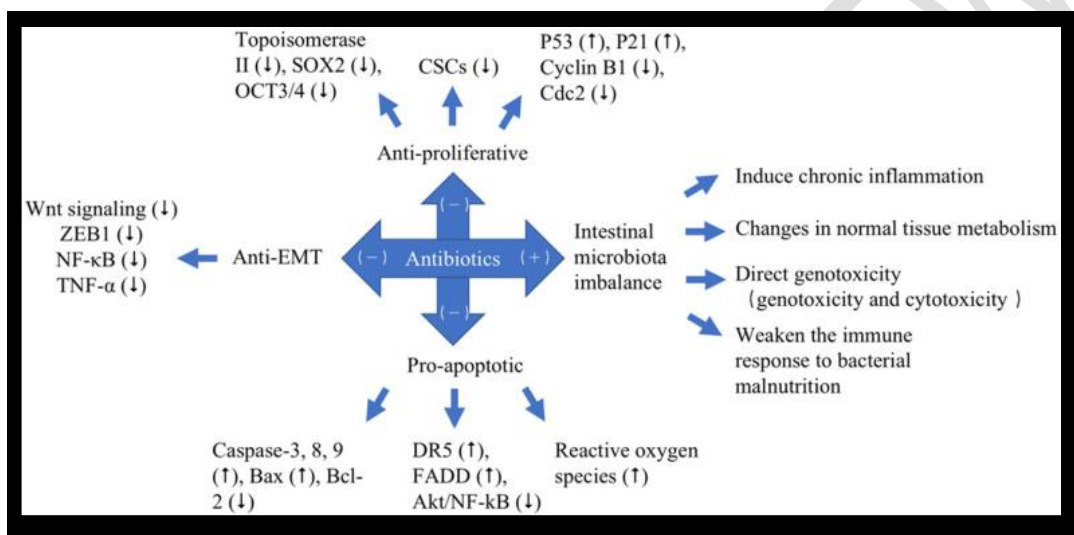


Figure 4: The mechanisms of Anticancer antibiotics [141].

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 cycle, as seen with cyclinon-specific drugs [142]. 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 [143]. 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 [144].

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 [145]. 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 [146]. 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. [147], [148]. Furthermore, ciprofloxacin derivatives caused G2/M phase arrest through a p53/p21 dependent pathway. Ciprofloxacin may thus have an anti-proliferative effect [149].

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 [141].

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 [150].

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 [151]. 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 [152].

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 [153]. Dead probiotics and their metabolites are also extremely important in tumor prevention and control [154].

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 [155].

Laboratory and animal studies demonstrate that probiotics, prebiotics, and synbiotics (a mix of probiotics) effectively prevent cancer [155].

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 [156].

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) [157]. 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 [158].

Anti-tumor effects of probiotics remain uncertain in a particular mechanism. Gut microbiota has several pathways in this phase that are considered to be essential. In order 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 [159].

Probiotics preserve the metabolic health of the other types of microflora in the intestines. When *E. coli* and *Clostridium perfringens* normally found in the intestine produce carcinogenic enzymes including b-glucuronidase and azoreductase [160].

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 [161], [162].

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) [163]. 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.

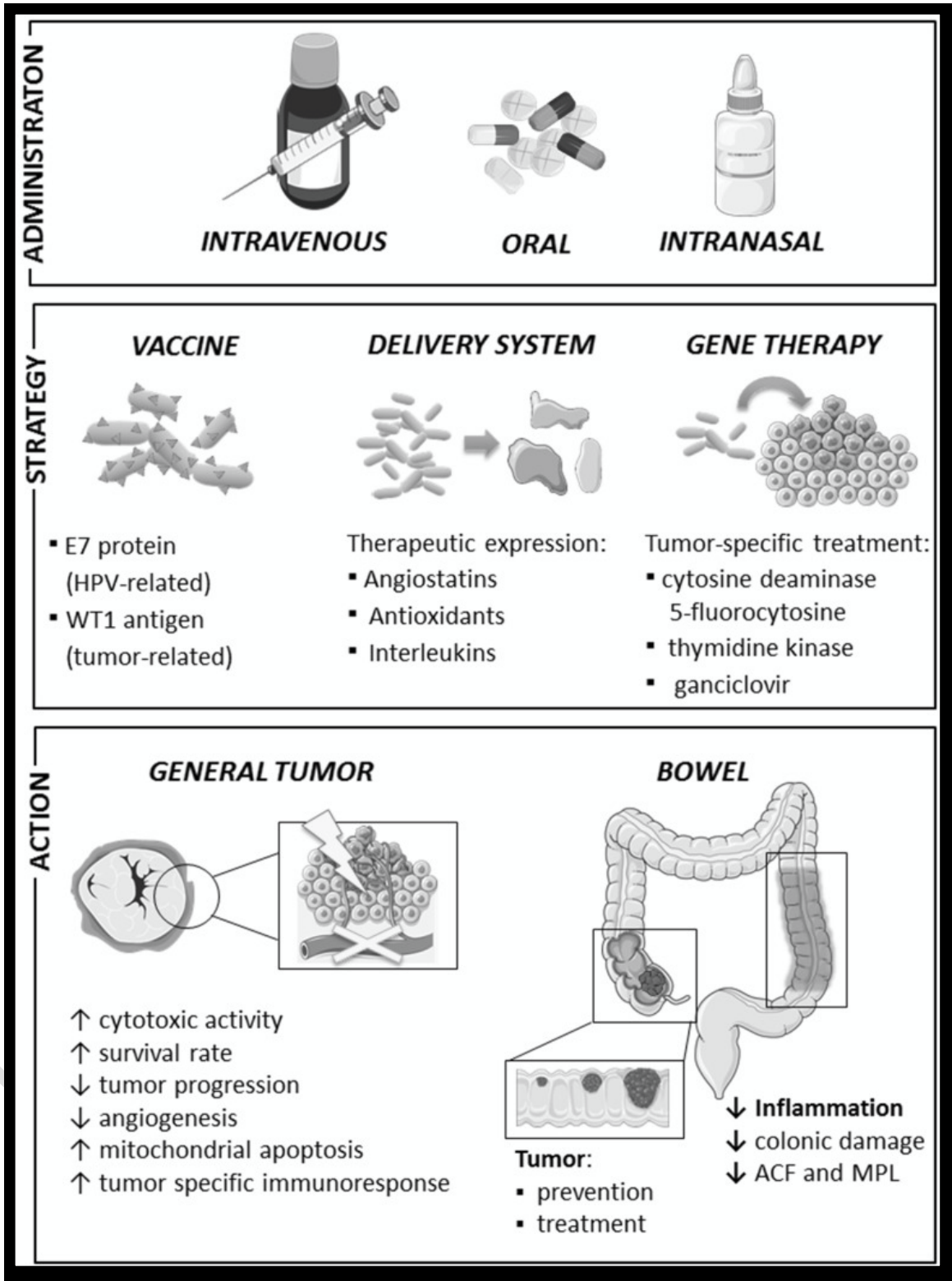


Figure 5: Possible treatment and cancer prevention use of probiotic bacteria [158].

8. References:

- [1] C. M. Robinson and J. K. Pfeiffer, "Viruses and the microbiota," *Annu. Rev. Virol.*, vol. 1, pp. 55–69, 2014.
- [2] J. K. Pfeiffer and H. W. Virgin, "Transkingdom control of viral infection and immunity in the mammalian intestine," *Science (80-.)*, vol. 351, no. 6270, 2016.
- [3] E. E. Ashu, J. Xu, and Z.-C. Yuan, "Bacteria in cancer therapeutics: a framework for effective therapeutic bacterial screening and identification," *J. Cancer*, vol. 10, no. 8, p. 1781, 2019.
- [4] K. A. Hoadley *et al.*, "Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin," *Cell*, vol. 158, no. 4, pp. 929–944, 2014.
- [5] W. Torres *et al.*, "Bacteria in cancer therapy: beyond immunostimulation," *J. Cancer Metastasis Treat.*, vol. 4, 2018.
- [6] G. A. Ogunrinola, J. O. Oyewale, O. O. Oshamika, and G. I. Olasehinde, "The human microbiome and its impacts on health," *Int. J. Microbiol.*, vol. 2020, 2020.
- [7] C. M. Whisner and C. A. Aktipis, "The role of the microbiome in cancer initiation and progression: how microbes and cancer cells utilize excess energy and promote one another's growth," *Curr. Nutr. Rep.*, vol. 8, no. 1, pp. 42–51, 2019.
- [8] R. Francescone and D. B. Vendramini-Costa, "Microbiome and cancer," *Hum. Microbiota Chronic Dis. Dysbiosis as a Cause Hum. Pathol.*, p. 371, 2016.
- [9] H. Armstrong, M. Bording-Jorgensen, S. Dijk, and E. Wine, "The complex interplay between chronic inflammation, the microbiome, and cancer: understanding disease progression and what we can do to prevent it," *Cancers (Basel)*, vol. 10, no. 3, p. 83, 2018.
- [10] B. A. Helmink, M. A. W. Khan, A. Hermann, V. Gopalakrishnan, and J. A. Wargo, "The microbiome, cancer, and cancer therapy," *Nat. Med.*, vol. 25, no. 3, pp. 377–388, 2019.
- [11] T. Kovács, E. Mikó, G. Ujlaki, Z. Sári, and P. Bai, "The microbiome as a component of the tumor microenvironment," *Tumor Microenviron.*, pp. 137–153, 2020.
- [12] M. Hatakeyama, "Oncogenic mechanisms of the Helicobacter pylori CagA protein," *Nat. Rev. Cancer*, vol. 4, no. 9, pp. 688–694, 2004.
- [13] M. R. Rubinstein, X. Wang, W. Liu, Y. Hao, G. Cai, and Y. W. Han, "Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/ β -catenin signaling via its FadA adhesin," *Cell Host Microbe*, vol. 14, no. 2, pp. 195–206, 2013.
- [14] J. C. Arthur *et al.*, "Intestinal inflammation targets cancer-inducing activity of the microbiota," *Science (80-.)*, vol. 338, no. 6103, pp. 120–123, 2012.
- [15] W. Song, A. C. Anselmo, and L. Huang, "Nanotechnology intervention of the microbiome for cancer therapy," *Nat. Nanotechnol.*, vol. 14, no. 12, pp. 1093–1103, 2019.
- [16] L. Turnbough and L. Wilson, "'Take your medicine': nonadherence issues in patients with

- ulcerative colitis,” *Gastroenterol. Nurs.*, vol. 30, no. 3, pp. 212–217, 2007.
- [17] H. Chial, “DNA sequencing technologies key to the Human Genome Project,” *Nat. Educ.*, vol. 1, no. 1, 2008.
- [18] J. K. Goodrich *et al.*, “Conducting a microbiome study,” *Cell*, vol. 158, no. 2, pp. 250–262, 2014.
- [19] B. A. Methé *et al.*, “A framework for human microbiome research,” *Nature*, vol. 486, no. 7402, p. 215, 2012.
- [20] G. M. Weinstock, “Genomic approaches to studying the human microbiota,” *Nature*, vol. 489, no. 7415, pp. 250–256, 2012.
- [21] E. A. Grice and J. A. Segre, “The skin microbiome,” *Nat. Rev. Microbiol.*, vol. 9, no. 4, pp. 244–253, 2011.
- [22] M. G. Surette, “The cystic fibrosis lung microbiome,” *Ann. Am. Thorac. Soc.*, vol. 11, no. Supplement 1, pp. S61–S65, 2014.
- [23] J. M. Beck, “Et aii The microbiome of the lung Transl,” *Res*, vol. 160, no. 4, pp. 258–266, 2012.
- [24] B. Ma, L. J. Forney, and J. Ravel, “Vaginal microbiome: rethinking health and disease,” *Annu. Rev. Microbiol.*, vol. 66, pp. 371–389, 2012.
- [25] C. Urbaniak *et al.*, “Microbiota of human breast tissue,” *Appl. Environ. Microbiol.*, vol. 80, no. 10, pp. 3007–3014, 2014.
- [26] P. B. Eckburg *et al.*, “Diversity of the human intestinal microbial flora,” *Science (80-.)*, vol. 308, no. 5728, pp. 1635–1638, 2005.
- [27] D. C. Savage, “Microbial ecology of the gastrointestinal tract,” *Annu. Rev. Microbiol.*, vol. 31, no. 1, pp. 107–133, 1977.
- [28] N. S. Chu and M. Favero, “The microbial flora of the gastrointestinal tract and the cleaning of flexible endoscopes,” *Gastrointest. Endosc. Clin. N. Am.*, vol. 10, no. 2, pp. 233–244, 2000.
- [29] T. Clavel, J. C. Gomes-Neto, I. Lagkouvardos, and A. E. Ramer-Tait, “Deciphering interactions between the gut microbiota and the immune system via microbial cultivation and minimal microbiomes,” *Immunol. Rev.*, vol. 279, no. 1, pp. 8–22, 2017.
- [30] E. Biagi *et al.*, “Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians,” *PLoS One*, vol. 5, no. 5, p. e10667, 2010.
- [31] M. G. Dominguez-Bello, M. J. Blaser, R. E. Ley, and R. Knight, “Development of the human gastrointestinal microbiota and insights from high-throughput sequencing,” *Gastroenterology*, vol. 140, no. 6, pp. 1713–1719, 2011.
- [32] S. A. Whiteside, H. Razvi, S. Dave, G. Reid, and J. P. Burton, “The microbiome of the urinary tract—a role beyond infection,” *Nat. Rev. Urol.*, vol. 12, no. 2, p. 81, 2015.
- [33] N. T. Mueller, E. Bakacs, J. Combellick, Z. Grigoryan, and M. G. Dominguez-Bello, “The

- infant microbiome development: mom matters,” *Trends Mol. Med.*, vol. 21, no. 2, pp. 109–117, 2015.
- [34] M. J. Claesson *et al.*, “Gut microbiota composition correlates with diet and health in the elderly,” *Nature*, vol. 488, no. 7410, pp. 178–184, 2012.
- [35] L. M. Cox and M. J. Blaser, “Antibiotics in early life and obesity,” *Nat. Rev. Endocrinol.*, vol. 11, no. 3, p. 182, 2015.
- [36] C. A. Thaiss, N. Zmora, M. Levy, and E. Elinav, “The microbiome and innate immunity,” *Nature*, vol. 535, no. 7610, pp. 65–74, 2016.
- [37] W. H. W. Tang and S. L. Hazen, “The gut microbiome and its role in cardiovascular diseases,” *Circulation*, vol. 135, no. 11, pp. 1008–1010, 2017.
- [38] S. Thomas *et al.*, “The host microbiome regulates and maintains human health: a primer and perspective for non-microbiologists,” *Cancer Res.*, vol. 77, no. 8, pp. 1783–1812, 2017.
- [39] J. M. Anderson and C. M. Van Itallie, “Physiology and function of the tight junction,” *Cold Spring Harb. Perspect. Biol.*, vol. 1, no. 2, p. a002584, 2009.
- [40] M. F. Moffatt and W. O. C. M. Cookson, “The lung microbiome in health and disease,” *Clin. Med. (Northfield. Il.)*, vol. 17, no. 6, p. 525, 2017.
- [41] R. Faner *et al.*, “The microbiome in respiratory medicine: current challenges and future perspectives,” *Eur. Respir. J.*, vol. 49, no. 4, 2017.
- [42] M. Hilty *et al.*, “Disordered microbial communities in asthmatic airways,” *PLoS One*, vol. 5, no. 1, p. e8578, 2010.
- [43] R. P. Dickson, J. R. Erb-Downward, F. J. Martinez, and G. B. Huffnagle, “The microbiome and the respiratory tract,” *Annu. Rev. Physiol.*, vol. 78, pp. 481–504, 2016.
- [44] M. J. Bull and N. T. Plummer, “Part 1: The human gut microbiome in health and disease,” *Integr. Med. A Clin. J.*, vol. 13, no. 6, p. 17, 2014.
- [45] A. A. Teitelbaum, M. G. Gareau, J. Jury, P. C. Yang, and M. H. Perdue, “Chronic peripheral administration of corticotropin-releasing factor causes colonic barrier dysfunction similar to psychological stress,” *Am. J. Physiol. Liver Physiol.*, vol. 295, no. 3, pp. G452–G459, 2008.
- [46] C. V Sobol, “How microbiome impact on the cardiovascular system,” *J Clin Trial Cardiol*, vol. 1, p. 1411, 2014.
- [47] M. Jin, Z. Qian, J. Yin, W. Xu, and X. Zhou, “The role of intestinal microbiota in cardiovascular disease,” *J. Cell. Mol. Med.*, vol. 23, no. 4, pp. 2343–2350, 2019.
- [48] A. Clifford and G. S. Hoffman, “Evidence for a vascular microbiome and its role in vessel health and disease,” *Curr. Opin. Rheumatol.*, vol. 27, no. 4, pp. 397–405, 2015.
- [49] J. Li *et al.*, “Gut microbiota dysbiosis contributes to the development of hypertension,” *Microbiome*, vol. 5, no. 1, pp. 1–19, 2017.

- [50] Z. Y. Kho and S. K. Lal, “The human gut microbiome—a potential controller of wellness and disease,” *Front. Microbiol.*, vol. 9, p. 1835, 2018.
- [51] J. Peng, X. Xiao, M. Hu, and X. Zhang, “Interaction between gut microbiome and cardiovascular disease,” *Life Sci.*, vol. 214, pp. 153–157, 2018.
- [52] I. M. Aragón *et al.*, “The urinary tract microbiome in health and disease,” *Eur. Urol. Focus*, vol. 4, no. 1, pp. 128–138, 2018.
- [53] W. H. W. Tang *et al.*, “Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease,” *Circ. Res.*, vol. 116, no. 3, pp. 448–455, 2015.
- [54] R. L. Siegel, K. D. Miller, and A. Jemal, “Cancer statistics, 2019,” *CA. Cancer J. Clin.*, vol. 69, no. 1, pp. 7–34, 2019.
- [55] K. D. Miller *et al.*, “Cancer statistics for hispanics/latinos, 2018,” *CA. Cancer J. Clin.*, vol. 68, no. 6, pp. 425–445, 2018.
- [56] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, “Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries,” *CA. Cancer J. Clin.*, vol. 68, no. 6, pp. 394–424, 2018.
- [57] C. De Martel *et al.*, “Global burden of cancers attributable to infections in 2008: a review and synthetic analysis,” *Lancet Oncol.*, vol. 13, no. 6, pp. 607–615, 2012.
- [58] M. M. Azevedo, C. Pina-Vaz, and F. Baltazar, “Microbes and Cancer: Friends or Faux?,” *Int. J. Mol. Sci.*, vol. 21, no. 9, p. 3115, Apr. 2020.
- [59] B. J. Marshall, “*Helicobacter pylori*: the etiologic agent for peptic ulcer,” *Jama*, vol. 274, no. 13, pp. 1064–1066, 1995.
- [60] A. D. Kostic *et al.*, “Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma,” *Genome Res.*, vol. 22, no. 2, pp. 292–298, 2012.
- [61] A. N. McCoy, F. Araujo-Perez, A. Azcarate-Peril, J. J. Yeh, R. S. Sandler, and T. O. Keku, “*Fusobacterium* is associated with colorectal adenomas,” *PLoS One*, vol. 8, no. 1, p. e53653, 2013.
- [62] M. Castellarin *et al.*, “*Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma,” *Genome Res.*, vol. 22, no. 2, pp. 299–306, 2012.
- [63] C. Urbaniak, G. B. Gloor, M. Brackstone, L. Scott, M. Tangney, and G. Reid, “The microbiota of breast tissue and its association with breast cancer,” *Appl. Environ. Microbiol.*, vol. 82, no. 16, pp. 5039–5048, 2016.
- [64] J. L. Round and S. K. Mazmanian, “The gut microbiota shapes intestinal immune responses during health and disease,” *Nat. Rev. Immunol.*, vol. 9, no. 5, pp. 313–323, 2009.
- [65] M. F. Vaezi *et al.*, “CagA-positive strains of *Helicobacter pylori* may protect against Barrett’s esophagus,” *Am. J. Gastroenterol.*, vol. 95, no. 9, pp. 2206–2211, 2000.

- [66] L. A. Fischbach *et al.*, “Association between *Helicobacter pylori* and Barrett’s Esophagus: A Case–Control Study,” *Am. J. Gastroenterol.*, vol. 109, no. 3, p. 357, 2014.
- [67] Z. Pei, E. J. Bini, L. Yang, M. Zhou, F. Francois, and M. J. Blaser, “Bacterial biota in the human distal esophagus,” *Proc. Natl. Acad. Sci.*, vol. 101, no. 12, pp. 4250–4255, 2004.
- [68] L. Yang, X. Lu, C. W. Nossa, F. Francois, R. M. Peek, and Z. Pei, “Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome,” *Gastroenterology*, vol. 137, no. 2, pp. 588–597, 2009.
- [69] L. Mira-Pascual *et al.*, “Microbial mucosal colonic shifts associated with the development of colorectal cancer reveal the presence of different bacterial and archaeal biomarkers,” *J. Gastroenterol.*, vol. 50, no. 2, pp. 167–179, 2015.
- [70] R. L. Warren *et al.*, “Co-occurrence of anaerobic bacteria in colorectal carcinomas,” *Microbiome*, vol. 1, no. 1, pp. 1–12, 2013.
- [71] A. D. Kostic *et al.*, “*Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment,” *Cell Host Microbe*, vol. 14, no. 2, pp. 207–215, 2013.
- [72] S. Bullman *et al.*, “Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer,” *Science (80-.)*, vol. 358, no. 6369, pp. 1443–1448, 2017.
- [73] L. T. Geller *et al.*, “Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine,” *Science (80-.)*, vol. 357, no. 6356, pp. 1156–1160, 2017.
- [74] C. Xuan *et al.*, “Microbial dysbiosis is associated with human breast cancer,” *PLoS One*, vol. 9, no. 1, p. e83744, 2014.
- [75] A. A. Chan *et al.*, “Characterization of the microbiome of nipple aspirate fluid of breast cancer survivors,” *Sci. Rep.*, vol. 6, no. 1, pp. 1–11, 2016.
- [76] R. J. Cohen, B. A. Shannon, J. E. McNEAL, T. O. M. Shannon, and K. L. Garrett, “*Propionibacterium acnes* associated with inflammation in radical prostatectomy specimens: a possible link to cancer evolution?,” *J. Urol.*, vol. 173, no. 6, pp. 1969–1974, 2005.
- [77] L. F. Fehri *et al.*, “Prevalence of *Propionibacterium acnes* in diseased prostates and its inflammatory and transforming activity on prostate epithelial cells,” *Int. J. Med. Microbiol.*, vol. 301, no. 1, pp. 69–78, 2011.
- [78] K. S. Sfanos, J. Sauvageot, H. L. Fedor, J. D. Dick, A. M. De Marzo, and W. B. Isaacs, “A molecular analysis of prokaryotic and viral DNA sequences in prostate tissue from patients with prostate cancer indicates the presence of multiple and diverse microorganisms,” *Prostate*, vol. 68, no. 3, pp. 306–320, 2008.
- [79] H.-L. Gong *et al.*, “The composition of microbiome in larynx and the throat biodiversity between laryngeal squamous cell carcinoma patients and control population,” *PLoS One*, vol. 8, no. 6, p. e66476, 2013.

- [80] H. Liang *et al.*, “Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: a systematic review,” *Int. J. cancer*, vol. 125, no. 12, pp. 2936–2944, 2009.
- [81] V. Pilaniya, K. Gera, S. Kunal, and A. Shah, “Pulmonary tuberculosis masquerading as metastatic lung disease,” *Eur. Respir. Rev.*, vol. 25, no. 139, pp. 97–98, 2016.
- [82] L. M. F. Merlo, J. W. Pepper, B. J. Reid, and C. C. Maley, “Cancer as an evolutionary and ecological process,” *Nat. Rev. cancer*, vol. 6, no. 12, pp. 924–935, 2006.
- [83] K. Polyak, I. Haviv, and I. G. Campbell, “Co-evolution of tumor cells and their microenvironment,” *Trends Genet.*, vol. 25, no. 1, pp. 30–38, 2009.
- [84] D. F. Quail and J. A. Joyce, “Microenvironmental regulation of tumor progression and metastasis,” *Nat. Med.*, vol. 19, no. 11, pp. 1423–1437, 2013.
- [85] L. M. Coussens and Z. Werb, “Inflammation and cancer,” *Nature*, vol. 420, no. 6917, pp. 860–867, 2002.
- [86] S. V Rajagopala *et al.*, “The human microbiome and cancer,” *Cancer Prev. Res.*, vol. 10, no. 4, pp. 226–234, 2017.
- [87] A. Müller, “Multistep activation of the *Helicobacter pylori* effector CagA,” *J. Clin. Invest.*, vol. 122, no. 4, pp. 1192–1195, 2012.
- [88] T. Jess, C. Rungoe, and L. Peyrin-Biroulet, “Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies,” *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.*, vol. 10, no. 6, pp. 639–645, Jun. 2012.
- [89] K. Bergstrom *et al.*, “Defective Intestinal Mucin-Type O-Glycosylation Causes Spontaneous Colitis-Associated Cancer in Mice,” *Gastroenterology*, vol. 151, no. 1, pp. 152-164.e11, Jul. 2016.
- [90] W. Xu, Z. Liu, Q. Bao, and Z. Qian, “Viruses, Other Pathogenic Microorganisms and Esophageal Cancer,” *Gastrointest. tumors*, vol. 2, no. 1, pp. 2–13, May 2015.
- [91] J. S. Pagano *et al.*, “Infectious agents and cancer: criteria for a causal relation,” in *Seminars in cancer biology*, 2004, vol. 14, no. 6, pp. 453–471.
- [92] P. Pimentel-Nunes *et al.*, “Increased expression of toll-like receptors (TLR) 2, 4 and 5 in gastric dysplasia,” *Pathol. Oncol. Res.*, vol. 17, no. 3, pp. 677–683, Sep. 2011.
- [93] E. Buc *et al.*, “High prevalence of mucosa-associated *E. coli* producing cyclomodulin and genotoxin in colon cancer,” *PLoS One*, vol. 8, no. 2, p. e56964, 2013.
- [94] G. Dalmaso, A. Cougnoux, J. Delmas, A. Darfeuille-Michaud, and R. Bonnet, “The bacterial genotoxin colibactin promotes colon tumor growth by modifying the tumor microenvironment,” *Gut Microbes*, vol. 5, no. 5, pp. 675–680, 2014.
- [95] C. M. Dejea *et al.*, “Microbiota organization is a distinct feature of proximal colorectal cancers,” *Proc. Natl. Acad. Sci.*, vol. 111, no. 51, pp. 18321–18326, 2014.

- [96] M. Koepfel, F. Garcia-Alcalde, F. Glowinski, P. Schlaermann, and T. F. Meyer, "Helicobacter pylori infection causes characteristic DNA damage patterns in human cells," *Cell Rep.*, vol. 11, no. 11, pp. 1703–1713, 2015.
- [97] L. E. Wroblewski and R. M. Peek, "Helicobacter pylori in gastric carcinogenesis: mechanisms," *Gastroenterol. Clin.*, vol. 42, no. 2, pp. 285–298, 2013.
- [98] D. M. Hardbower, T. de Sablet, R. Chaturvedi, and K. T. Wilson, "Chronic inflammation and oxidative stress: the smoking gun for Helicobacter pylori-induced gastric cancer?," *Gut Microbes*, vol. 4, no. 6, pp. 475–481, 2013.
- [99] L.-X. Yu *et al.*, "Endotoxin accumulation prevents carcinogen-induced apoptosis and promotes liver tumorigenesis in rodents.," *Hepatology*, vol. 52, no. 4, pp. 1322–1333, Oct. 2010.
- [100] S. Yoshimoto *et al.*, "Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome," *Nature*, vol. 499, no. 7456, pp. 97–101, 2013.
- [101] R. M. J. Peek and M. J. Blaser, "Helicobacter pylori and gastrointestinal tract adenocarcinomas.," *Nat. Rev. Cancer*, vol. 2, no. 1, pp. 28–37, Jan. 2002.
- [102] J. Abed *et al.*, "Fap2 Mediates Fusobacterium nucleatum Colorectal Adenocarcinoma Enrichment by Binding to Tumor-Expressed Gal-GalNAc.," *Cell Host Microbe*, vol. 20, no. 2, pp. 215–225, Aug. 2016.
- [103] A. Koh, F. De Vadder, P. Kovatcheva-Datchary, and F. Bäckhed, "From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites.," *Cell*, vol. 165, no. 6, pp. 1332–1345, Jun. 2016.
- [104] P. Bu *et al.*, "Aldolase B-Mediated Fructose Metabolism Drives Metabolic Reprogramming of Colon Cancer Liver Metastasis.," *Cell Metab.*, vol. 27, no. 6, pp. 1249–1262.e4, Jun. 2018.
- [105] Y. Belkaid and T. W. Hand, "Role of the microbiota in immunity and inflammation," *Cell*, vol. 157, no. 1, pp. 121–141, Mar. 2014.
- [106] A. Iwasaki and B. L. Kelsall, "Freshly isolated Peyer's patch, but not spleen, dendritic cells produce interleukin 10 and induce the differentiation of T helper type 2 cells," *J. Exp. Med.*, vol. 190, no. 2, pp. 229–240, 1999.
- [107] L. E. Smythies *et al.*, "Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity," *J. Clin. Invest.*, vol. 115, no. 1, pp. 66–75, 2005.
- [108] L. E. Smythies *et al.*, "Inflammation anergy in human intestinal macrophages is due to Smad-induced IκBα expression and NF-κB inactivation," *J. Biol. Chem.*, vol. 285, no. 25, pp. 19593–19604, 2010.
- [109] A. Khosravi *et al.*, "Gut microbiota promote hematopoiesis to control bacterial infection," *Cell Host Microbe*, vol. 15, no. 3, pp. 374–381, 2014.
- [110] D. Zhang and P. S. Frenette, "Cross talk between neutrophils and the microbiota," *Blood*,

- vol. 133, no. 20, pp. 2168–2177, May 2019.
- [111] N. Satoh-Takayama *et al.*, “Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense,” *Immunity*, vol. 29, no. 6, pp. 958–970, 2008.
- [112] A. J. Macpherson, M. M. Martinic, and N. Harris, “The functions of mucosal T cells in containing the indigenous commensal flora of the intestine,” *Cell. Mol. Life Sci. C.*, vol. 59, no. 12, pp. 2088–2096, 2002.
- [113] P. Brandtzaeg *et al.*, “Immunobiology and immunopathology of human gut mucosa: humoral immunity and intraepithelial lymphocytes,” *Gastroenterology*, vol. 97, no. 6, pp. 1562–1584, 1989.
- [114] X. Yin *et al.*, “Direct costs of both inpatient and outpatient care for all type cancers: The evidence from Beijing, China,” *Cancer Med.*, vol. 8, no. 6, pp. 3250–3260, 2019.
- [115] A. M. O’Hara and F. Shanahan, “The gut flora as a forgotten organ,” *EMBO Rep.*, vol. 7, no. 7, pp. 688–693, 2006.
- [116] S. Temraz, F. Nassar, R. Nasr, M. Charafeddine, D. Mukherji, and A. Shamseddine, “Gut Microbiome: A Promising Biomarker for Immunotherapy in Colorectal Cancer,” *Int. J. Mol. Sci.*, vol. 20, no. 17, p. 4155, Aug. 2019.
- [117] M. Vétizou *et al.*, “Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota,” *Science (80-.)*, vol. 350, no. 6264, pp. 1079–1084, 2015.
- [118] S. Viaud *et al.*, “The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide,” *Science (80-.)*, vol. 342, no. 6161, pp. 971–976, 2013.
- [119] J. U. Peled *et al.*, “Intestinal microbiota and relapse after hematopoietic-cell transplantation,” *J. Clin. Oncol.*, vol. 35, no. 15, p. 1650, 2017.
- [120] A. Lundin *et al.*, “Gut flora, Toll-like receptors and nuclear receptors: a tripartite communication that tunes innate immunity in large intestine,” *Cell. Microbiol.*, vol. 10, no. 5, pp. 1093–1103, 2008.
- [121] W. Li, Y. Deng, Q. Chu, and P. Zhang, “Gut microbiome and cancer immunotherapy,” *Cancer Lett.*, vol. 447, pp. 41–47, 2019.
- [122] G. Kroemer and L. Zitvogel, “The breakthrough of the microbiota,” *Nat. Rev. Immunol.*, vol. 18, no. 2, pp. 87–88, 2018.
- [123] D. S. Chen and I. Mellman, “Elements of cancer immunity and the cancer-immune set point,” *Nature*, vol. 541, no. 7637, pp. 321–330, 2017.
- [124] J. Larkin *et al.*, “Combined nivolumab and ipilimumab or monotherapy in untreated melanoma,” *N. Engl. J. Med.*, vol. 373, no. 1, pp. 23–34, 2015.
- [125] C. Y. Ok and K. H. Young, “Checkpoint inhibitors in hematological malignancies,” *J. Hematol. Oncol.*, vol. 10, no. 1, pp. 1–16, 2017.
- [126] B. Routy *et al.*, “Gut microbiome influences efficacy of PD-1–based immunotherapy

- against epithelial tumors,” *Science* (80-.), vol. 359, no. 6371, pp. 91–97, 2018.
- [127] A. E. Frankel *et al.*, “Metagenomic shotgun sequencing and unbiased metabolomic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients,” *Neoplasia*, vol. 19, no. 10, pp. 848–855, 2017.
- [128] N. Chaput *et al.*, “Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab,” *Ann. Oncol.*, vol. 28, no. 6, pp. 1368–1379, 2017.
- [129] K. Dubin *et al.*, “Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis,” *Nat. Commun.*, vol. 7, no. 1, pp. 1–8, 2016.
- [130] J. L. Round and S. K. Mazmanian, “Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota,” *Proc. Natl. Acad. Sci.*, vol. 107, no. 27, pp. 12204–12209, 2010.
- [131] D. Zella *et al.*, “Mycoplasma promotes malignant transformation in vivo, and its DnaK, a bacterial chaperone protein, has broad oncogenic properties,” *Proc. Natl. Acad. Sci.*, vol. 115, no. 51, pp. E12005–E12014, 2018.
- [132] C. Carbone *et al.*, “Lung and gut microbiota as potential hidden driver of immunotherapy efficacy in lung cancer,” *Mediators Inflamm.*, vol. 2019, 2019.
- [133] G. Redelman-Sidi, M. S. Glickman, and B. H. Bochner, “The mechanism of action of BCG therapy for bladder cancer—a current perspective,” *Nat. Rev. Urol.*, vol. 11, no. 3, p. 153, 2014.
- [134] C. A. Rentsch *et al.*, “Bacillus Calmette-Guérin strain differences have an impact on clinical outcome in bladder cancer immunotherapy,” *Eur. Urol.*, vol. 66, no. 4, pp. 677–688, 2014.
- [135] J. Vande Voorde, J. Balzarini, and S. Liekens, “Mycoplasmas and cancer: focus on nucleoside metabolism,” *EXCLI J.*, vol. 13, p. 300, 2014.
- [136] Q. F. Gui, H. F. Lu, C. X. Zhang, Z. R. Xu, and Y. H. Yang, “Well-balanced commensal microbiota contributes to anti-cancer response in a lung cancer mouse model,” *Genet Mol Res*, vol. 14, no. 2, pp. 5642–5651, 2015.
- [137] J. Barrios-González and A. Mejía, “Production of antibiotics and other commercially valuable secondary metabolites,” in *Current developments in solid-state fermentation*, Springer, 2008, pp. 302–336.
- [138] D. Xia *et al.*, “Over-expression of CHAF1A in Epithelial Ovarian Cancer can promote cell proliferation and inhibit cell apoptosis,” *Biochem. Biophys. Res. Commun.*, vol. 486, no. 1, pp. 191–197, 2017.
- [139] S. Saeidnia, *New approaches to natural anticancer drugs*. Springer, 2015.
- [140] G. M. Cragg and D. J. Newman, “Natural products drug discovery and development at the United States National Cancer Institute,” in *Drug Discovery and Traditional Chinese*

- Medicine*, Springer, 2001, pp. 19–32.
- [141] Y. Gao *et al.*, “Antibiotics for cancer treatment: A double-edged sword,” *J. Cancer*, vol. 11, no. 17, pp. 5135–5149, Jun. 2020.
- [142] Z. Xiao, B. Sperl, A. Ullrich, and P. Knyazev, “Metformin and salinomycin as the best combination for the eradication of NSCLC monolayer cells and their alveospheres (cancer stem cells) irrespective of EGFR, KRAS, EML4/ALK and LKB1 status,” *Oncotarget*, vol. 5, no. 24, p. 12877, 2014.
- [143] J. Zhou *et al.*, “Salinomycin induces apoptosis in cisplatin-resistant colorectal cancer cells by accumulation of reactive oxygen species,” *Toxicol. Lett.*, vol. 222, no. 2, pp. 139–145, 2013.
- [144] P. Pratheeshkumar and G. Kuttan, “Oleanolic acid induces apoptosis by modulating p53, Bax, Bcl-2 and caspase-3 gene expression and regulates the activation of transcription factors and cytokine profile in B16F,” *J. Environ. Pathol. Toxicol. Oncol.*, vol. 30, no. 1, 2011.
- [145] S. Young, W. J. Kim, D. J. Yu, H. S. Gang, and S. R. Jang, “Synthesis and antitumor activity of new anthracycline analogues,” *Bull. Korean Chem. Soc.*, vol. 22, no. 9, pp. 963–968, 2001.
- [146] J. J. Barlow, M. S. Piver, J. T. Chuang, E. P. Cortes, T. Ohnuma, and J. F. Holland, “Adriamycin and bleomycin, alone and in combination, in gynecologic cancers,” *Cancer*, vol. 32, no. 4, pp. 735–743, 1973.
- [147] A. Beberok, D. Wrzeźniok, Z. Rzepka, M. Respondek, and E. Buszman, “Ciprofloxacin triggers the apoptosis of human triple-negative breast cancer MDA-MB-231 cells via the p53/Bax/Bcl-2 signaling pathway,” *Int. J. Oncol.*, vol. 52, no. 5, pp. 1727–1737, 2018.
- [148] A. Beberok *et al.*, “Ciprofloxacin-mediated induction of S-phase cell cycle arrest and apoptosis in COLO829 melanoma cells,” *Pharmacol. Reports*, vol. 70, no. 1, pp. 6–13, 2018.
- [149] H. H. H. Mohammed, A. A. Abd El-Hafeez, S. H. Abbas, E.-S. M. N. Abdelhafez, and G. E.-D. A. Abuo-Rahma, “New antiproliferative 7-(4-(N-substituted carbamoylmethyl) piperazin-1-yl) derivatives of ciprofloxacin induce cell cycle arrest at G2/M phase,” *Bioorg. Med. Chem.*, vol. 24, no. 19, pp. 4636–4646, 2016.
- [150] J. Fessler, V. Matson, and T. F. Gajewski, “Exploring the emerging role of the microbiome in cancer immunotherapy,” *J. Immunother. cancer*, vol. 7, no. 1, pp. 1–15, 2019.
- [151] S. Raguz and E. Yagüe, “Resistance to chemotherapy: new treatments and novel insights into an old problem,” *Br. J. Cancer*, vol. 99, no. 3, pp. 387–391, 2008.
- [152] S. Vivarelli *et al.*, “Gut microbiota and cancer: from pathogenesis to therapy,” *Cancers (Basel)*, vol. 11, no. 1, p. 38, 2019.
- [153] P. W. O’Toole, J. R. Marchesi, and C. Hill, “Next-generation probiotics: the spectrum from probiotics to live biotherapeutics,” *Nat. Microbiol.*, vol. 2, no. 5, pp. 1–6, 2017.

- [154] B. S. Rasouli, A. Ghadimi-Darsajini, R. Nekouian, and G.-R. Iragian, “In vitro activity of probiotic *Lactobacillus reuteri* against gastric cancer progression by downregulation of urokinase plasminogen activator/urokinase plasminogen activator receptor gene expression,” *J. Cancer Res. Ther.*, vol. 13, no. 2, p. 246, 2017.
- [155] M. Raman *et al.*, “Potential of probiotics, prebiotics and synbiotics for management of colorectal cancer,” *Gut Microbes*, vol. 4, no. 3, pp. 181–192, 2013.
- [156] P. J. Harris and L. R. Ferguson, “Dietary fibre: its composition and role in protection against colorectal cancer,” *Mutat. Res. Mol. Mech. Mutagen.*, vol. 290, no. 1, pp. 97–110, 1993.
- [157] B. R. Goldin and S. L. Gorbach, “Effect of *Lactobacillus acidophilus* dietary supplements on 1, 2-dimethylhydrazine dihydrochloride-induced intestinal cancer in rats,” *J. Natl. Cancer Inst.*, vol. 64, no. 2, pp. 263–265, 1980.
- [158] A. Górška, D. Przystupski, M. J. Niemczura, and J. Kulbacka, “Probiotic Bacteria: A Promising Tool in Cancer Prevention and Therapy,” *Curr. Microbiol.*, vol. 76, no. 8, pp. 939–949, Aug. 2019.
- [159] W. Jia, G. Xie, and W. Jia, “Bile acid–microbiota crosstalk in gastrointestinal inflammation and carcinogenesis,” *Nat. Rev. Gastroenterol. Hepatol.*, vol. 15, no. 2, p. 111, 2018.
- [160] K. Hirayama and J. Rafter, “The role of probiotic bacteria in cancer prevention,” *Microbes Infect.*, vol. 2, no. 6, pp. 681–686, 2000.
- [161] F. Faridnia, A. Hussin, N. Saari, S. Mustafa, L. Yee, and M. Manap, “In vitro binding of mutagenic heterocyclic aromatic amines by *Bifidobacterium pseudocatenulatum* G4,” *Benef. Microbes*, vol. 1, no. 2, pp. 149–154, 2010.
- [162] A. Nowak and Z. Libudzisz, “Ability of probiotic *Lactobacillus casei* DN 114001 to bind or/and metabolise heterocyclic aromatic amines in vitro,” *Eur. J. Nutr.*, vol. 48, no. 7, pp. 419–427, 2009.
- [163] J. Wells, “Mucosal vaccination and therapy with genetically modified lactic acid bacteria,” *Annu. Rev. Food Sci. Technol.*, vol. 2, pp. 423–445, 2011.