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The Role of the Microbiome in Cancer and the Development of Cancer Therapeutics

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Abstract

Cancer is caused by a compilation of hereditary and environmental factors. In the past decade, next-generation sequencing has revealed the extent to which the microbiome influences the maintenance of homeostasis and therefore the prevention of diseases such as cancer. Current research efforts explore the interaction between cancer and the microbiome, and the results are anticipated to transform how clinicians approach cancer treatment. There is a plausible transition from the use of human genetic biomarkers to microbiomic biomarkers for genomic diagnostics. Considering the expanding knowledge of the ways in which the microbiome can affect the development of cancer, clinicians treating cancer patients should be considerate of how the microbiome can influence the host-drug or microbiome-cancer interactions. Recognition of the importance of the microbiome within the field of oncology is pertinent to understanding and furthering cancer development and treatment.

Keywords

Microbiome; Cancer therapeutics; Leukemia; Breast cancer, Gastric cancer; Colorectal cancer; Skin cancer

Introduction

An individual's likelihood to develop cancer or respond to heterogeneous prescribed treatments for their cancer does not depend solely on the individual's genome. The environment that a person lives in can play a very important role in the development and persistence of cancer. Until recently, the environment within a patient was not considered when analyzing the longevity and treatment of cancer patients. The fields of cancer pharmacology and microbiology have become entangled within the last decade. next-generation sequencing has expedited this process by allowing researchers to identify the individual constituents and the overall complexity of the microbiome.

The holobiont is a composite of all the cells on and within our bodies. This concept is not restricted to human cells, but rather incorporates all present populations of bacteria, fungi, and viruses [1]. Researchers are investigating the holobiont as a tool to monitor cancer development and treatment. Our bodies are ecosystems that support mutualistic relationships with the billions of other organisms that live on and within us. The holobiome is a term which refers to the combination of all the genomes of the components that make up the holobiont [2]. The human genome can regulate the expression of the microbial genome, and *vice versa*. Additionally, bacterial metabolites produced on or within the human body can influence both normal cells and cancer cells. The consequences of such interactions may determine how cancer cells respond to chemotherapy, while the microbiome itself can prevent or promote cancer development.

Therefore, the composition of a patient's microbiome may function as a useful biomarker in predicting how a patient may respond to treatments, or combinations of treatments.

Leukemia

Dysbiosis, or the maladaptation and imbalance of bacteria present on or within the body, is correlated with decreasing levels of overall cancer survival and increased risk for infection [3]. There are differing perspectives regarding if dysbiosis causes cancer or if cancer causes dysbiosis, but nonetheless the two conditions are related to each other. This correlation is evident with leukemia and bacteremia (Table 1). Leukemia is a hematological malignancy that causes a population of immature white blood cells to clonally expand in the

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Bacterial Strains Associated with the Malignancy	Details of Roles in Development and/or Treatment
Lactic acid bacteria	Supplementation of prebiotics may foster increased growth of the bacteria, leading to increased production of the onco-suppressive metabolite butyrate. This metabolite may be used as a treatment for Irritable Bowel Syndrome to protect from bacterial strains entering the blood stream.
E. coli	Responsible for many bacteremia cases in AML and gastrointestinal leakage into the bloodstream.

Table 1: Bacterial strains and their roles in leukemia

bone marrow, thus inhibiting normal blood cell function. Bacteremia is a form of dysbiosis in which bacteria enter the blood stream [4]. TNFα-mediated disruptions of the intestinal barrier can induce the translocation of macromolecules from the gastrointestinal system to the vascular bed in murine models [5]. Induction chemotherapy can also break down the intestinal barrier, causing patients receiving hematopoietic stem cell transplants to have increased risk of bacteremia and acute graft-versus-host disease [6].

The utilization of intestinal barrier protection to prevent the translocation of bacteria from the gastrointestinal tract to the blood stream has been contemplated but not fully-investigated as a therapeutic for leukemia. Comparatively, Irritable Bowel Syndrome has been connected to leaky gut syndrome [7], but not to bacteria. Although the findings are difficult to interpret due to the use of various strains of probiotics, supplementation of lactic acid bacteria has been found to improve the phenotype of Irritable Bowel Syndrome and reduce leakage [7-9].

Probiotics or prebiotics have been used as mechanisms to up-regulate lactic acid bacteria and repair the gastrointestinal barrier [4,8]. The approach utilizing probiotics includes the administration of live bacteria, which, ironically, has been associated with a small percentage of bacteremia cases. Prebiotics are polysaccharides that are non-digestible by humans [10]. The supplementation of these prebiotics modifies the microbiome by up-regulating the bacterium that thrive on the polysaccharide substrate. Prebiotics have been utilized to up-regulate lactic acid bacteria and increase the production of butyrate [11,12]. Butyrate is a short chain fatty acid produced by the digestion of dietary fiber and complex carbohydrates. It can be an oncometabolite in mouse models of Lynch Syndrome, specifically of transgenic mice with mutations of the MMR gene family (*MLH1, MSH2, or PMS2*). In Lynch Syndrome model organisms, butyrate induces the proliferation of epithelial cells [13]. However, in MMR proficient models, butyrate can be utilized as an onco-suppressive metabolite. Therefore, in patients without MMR gene family mutations, butyrate should be considered as a potential cancer therapeutic. This alternating role of butyrate is termed the butyrate paradox. It is dependent upon the human host's genetic background [13], and should be considered if butyrate is utilized in leukemia drug development.

Antibiotics can also cause dysbiosis, thus adding an additional variable to consider when analyzing the interconnections between leukemia and dysbiosis. Many leukemia patients are treated with chemotherapeutics in combination with antibiotics. This can cause immunosuppression and disruption of the mucosal epithelium [4]. Disruption of an intestinal barrier's microbiome, and therefore the alpha diversity of the microbiome, implies the absence of commensal microorganisms that typically defend mucosal sites from pathogenic species.

This can in turn result in recurrent episodes of bacteremia. In the clinical setting, bacteremia is frequently correlated with intestinal barrier degradation and gut leakage [4]. Bacteria, and the toxins that the bacteria produce, can systemically spread throughout the body of a cancer patient if their gastrointestinal barrier is impaired. *E. coli* is responsible for many bacteremia cases in acute myeloid leukemia (AML) patients [14]. However, the so-called "leaky gut" of cancer patients has only recently been associated with AML patient bacteremia [5]. Alternative portals of bacteremia in leukemia patients include vascular catheters [15], the respiratory tract [16,17] and skin abrasions [18]. However, at State Clinical Hospital in Gdańsk, Poland, an estimated 72% of all bacteremia cases in the adult hematology clinic came from previously unknown sources [4]. Comparative 16S analysis of blood and bowel *E. coli* samples revealed that 24% of leukemia patient bacteremia cases of unknown origin were sourced from gastrointestinal leakage of *E. coli*. 19.1% of patients in the adult hematology clinic developed bacteremia, compared to the 1.6% of the rest of the hospital [4].

Loss of heterozygosity is also associated with increased risk due to the inability of one chromosome to compensate for mutations on the other [19]. Microbiome studies have revealed a similar loss of heterozygosity over time in cancer patient microbiomic profiles. This is otherwise referred to as decreased temporal variability or loss of diversity and it is associated with an increased risk of infection in cancer patients [3]. Loss of heterozygosity has been considered as a biomarker for leukemia patients to establish treatment plans. The associated form of dysbiosis does not stem from the absence of certain bacterium, but from the dysregulation of the native and commensal microbiota. It has been shown that AML patients have a higher likelihood to acquire an infection during induction chemotherapy if they have a low baseline gastrointestinal alpha diversity [20]. Comparatively, if the alpha diversity of both the oral and the gastrointestinal microbiome is low, the patient has a higher risk for infection within 90-days post-induction chemotherapy [20,21]. The fecal and buccal samples parallel each other in a trend of decreasing microbial diversity throughout a longitudinal analysis of patients undergoing induction chemotherapy [21]. A pattern of increased pathogenic genera domination events has also been observed throughout a longitudinal analysis [21]. Not surprisingly, when pathogenic bacteria dominate a patient's mucosal epithelium, the patient is more prone to infection [22]. Although not nearly as common, cases of increased diversity throughout induction chemotherapy have also been reported [21]. Oral and gastrointestinal sites are common origins of infection in immunocompromised patients [23,24]. Therefore, the temporal variability of the microbiome at both of those sites is imperative to the understanding and identification of biomarkers of alpha diversity for high and low risk infection groups. Microbiome composition could be used as a biomarker to identify leukemia patients that are more likely to develop infections throughout induction chemotherapy and less likely to have positive outcomes. Therefore, preventative actions could be taken including alternations in chemotherapeutic intervention, antimicrobial therapeutics, and microbiomic modification.

Breast Cancer

Breast cancer is one of the leading causes of cancer-related death in the United States, yet its etiology remains complex and perhaps elusive in certain situations [25]. This is especially so as the microbiome relates to breast cancer (Table 2). Interestingly, an increased incidence of breast cancer has been observed within patients that move from areas with low rates of breast cancer to areas with high rates of breast cancer [26]. This higher risk of breast cancer development can also be vertically transferred to offspring [26]. As previously discussed, cancer is sourced from a combination of genetic and environmental factors. Researchers have postulated that one of the possible environmental causes of this pattern could be a woman's microbiome [25]. A study investigated the breast

Bacterial Strains Associated with the Malignancy	Details of Roles in Development and/or Treatment
Staphylococcus epidermidis, *E. coli*	Strains isolated from the skin of cancerous breasts induced DNA double-stranded breaks in HeLa cells.
Lactobacillus helveticus R389	Oral administration of milk fermented by this bacterium has been correlated with reduced immune-regulation and breast tumor growth in murine models.
Lactobacillus casei CRL 431	Potential anti-metastatic and anti-angiogenic properties of milk fermented by this bacterium.
Lactobacillus plantarum	Potential for use for biotransformation of bioactive plants (such as ginseng) for treatment of many cancers, including breast cancer, as observed in studies of ulcerative colitis.

Table 2: Bacterial strains and their roles in breast cancer

Bacterial Strains Associated with the Malignancy	Details of Roles in Development and/or Treatment
Helicobacter pylori	• *H. pylori* classified as a class 1 carcinogen by the International Agency for Research on Cancer. • VacA protein produced by the bacterium causes pore formation in host cells, promoting vacuole formation and upregulation of apoptosis. • VacA protein binds to CD4+ T cells, sequestering NFAT in the cytoplasm and preventing activation of genes responsible for antigen-dependent T cell proliferation. Immunosuppression can moderate development and enhance the effects of gastric cancer. • CagA oncoprotein produced by *H. pylori* causes host morphological cell changes, loss of cell polarity, and resistance to apoptosis. • *H. pylori* peptidoglycan leads to stimulation of the PI3K/Akt signaling pathway in host cells, effecting actin cytoskeleton arrangements and upregulating genes involved in adenocarcinoma metaplasia. • CagA oncoprotein mediated over-stimulation of Wnt signaling pathway is observed in over 50% of gastric cancer cases.

Table 3: Bacterial strains and their roles in gastric cancer

microbial profiles of women effected by breast cancer verses healthy women. The microbiomic profiles of women with breast cancer had higher abundances of *Staphylococcus, Enterobacteriaceae,* and *Bacillus*, compared to controls. Species of *Staphylococcus epidermidis* and *Escherichia coli* isolated from the skin of the cancerous breasts caused genomic instability by inducing DNA double stranded breaks in HeLa cells [27]. Women with breast cancer also had decreased levels of lactic acid bacteria, as compared to women without breast cancer [27].

Oral administration of milk fermented by the lactic acid bacteria group member *Lactobacillus helveticus* R389, has been tested in mouse models and correlated with reduced growth of breast tumors and immune-regulation [28]. Further studies have established antimetastatic and anti-angiogenic properties of *Lactobacillus casei* CRL 431 fermented milk [29]. Interestingly, *Lactobacillus plantarum* fermentation of the red ginseng plant has also been used to increase the efficacy of bioactive compounds for the treatment of ulcerative colitis in mouse models [30]. Comparably to breast cancer, there was an observed discrepancy between the microbiomes of ulcerative colitis patients and healthy patients [31], including a lack of lactic acid bacteria [32]. It is predicted that non-responder mouse models did not have the necessary microbiome constituents to actively biotransform red ginseng. A combination of probiotics, including *Lactobacillus plantarum*, was utilized to convert red ginseng into an enhanced and activated form, thus reducing inflammation and the ulcerative colitis phenotype [30]. The utilization of probiotic fermentation has successfully been implemented with red ginseng treatments to induce an anti-diabetic effect as well [30]. Similar strategies of ethnobotanical biotransformation may be practical for the discovery of novel compounds for the treatment of cancer. The utilization of biotransformation is a promising approach to further cancer drug discovery efforts since dysbiosis is heavily correlated with cancer.

An innate metabolic connection between the microbiome and breast cancer has been established, as well. The bacterial secondary bile acid lithocholic acid was found to exhibit antiproliferative, anti-metastatic, and anti-angiogenic effects upon breast cancer *in vivo* and *in vitro*, without effecting primary cells [33]. The lithocholic acid mechanism of action was associated with TGR5 receptor activation [34]. However, the origin of the metabolite is still under speculation. Lithocholic acid can be produced both by the bacterium on the breast duct tissue and by the intestinal microflora [33,34]. This could imply a local, systemic, or combination effect. Finally, in the early stages of breast cancer, lithocholic acid levels and biosynthesis decrease which further supports its role in a biochemical pathway related to the prevention of breast cancer [33].

Gastric Cancer

Gastric adenocarcinoma is a prime and well-studied example for the role of the microbiome in cancer. Gastric adenocarcinoma, or cancer of the stomach, is a substantial cause of cancer-related deaths worldwide. Infection with the Helicobacter pylori bacteria is the leading risk factor for gastric cancer (Table 3), so it has been classified as a class 1 carcinogen by the International Agency for Research on Cancer [35]. Humans hold a long history with the *Helicobacter species*, with studies indicating the co-evolutionary history to span between 2,500 to 11,000 years ago. The *H. Pylori* bacterium is endemic to Africa and other third-world countries where the incidence of gastric cancer has been historically higher than in Western countries where exposure to the bacterium is less common [36]. Exposure to H. Pylori typically occurs during childhood, but the bacterium will remain with the individual as an underlying component of the gastric microbiota for many years without the development of clinical symptoms. In fact, the large majority of H. Pylori-infected individuals will live their entire life without developing gastric carcinoma or its preceding traits [37].

Despite the need for further research to incorporate all the environmental factors which can cause H. Pylori-mediated gastric

Bacterial Strains Associated with the Malignancy	Details of Roles in Development and/or Treatment
Coriobacteridae	• Overpopulation of this typically probiotic subclass is found on CRC patient "on-tumor" samples. • May produce butyrate, a potential anti-CRC compound which can upregulate apoptosis. • Butyrate may conversely function as an energy source for later-stage tumors and may suppress the immune system's inflammatory response.
Enterobacteriaceae	Lack of this potentially pathogenic subclass is found on CRC patient "on-tumor" samples.
Citrobacter rodentium	• Infection promotes CRC carcinogenesis in the APC ^{min} murine model. • Results in epithelial cell hyperproliferation in Crohn's Disease and ulcerative colitis in humans. Both conditions are linked to an increased CRC risk. • Can result in attaching and effacing lesions in the colon
Fuscobacterium	Correlation between this bacterium and the induction of inflammation, proliferation, and disease progression.

Table 4: Bacterial strains and their roles in colorectal cancer (CRC)

carcinogenesis, studies have explored the two main virulence factors of the bacterium. The two most well-known bacterial factors which play a role in gastric cancer development are VacA and CagA. The VacA gene is found in all strains of *H. Pylori*, but the levels of VacA protein production vary among individual strains. The VacA protein is excreted by the bacterium and causes pore formation in host cells. This effect promotes many events such as intracellular vacuole formation and upregulation of apoptosis. Additionally, the VacA protein binds to CD4+ T cells, preventing de-phosphorylation of NFAT to sequester the transcription factor in the cytoplasm so it cannot activate genes responsible for antigen dependent T cell proliferation [36,38]. These immunosuppressive traits of *H. Pylori* can enhance the effects and/or development of gastric cancer.

Additionally, more cytotoxic strains of *H. Pylori* possess the gene for production of the CagA protein, which is classified as a bacterial oncoprotein. This protein is produced by the bacterium, and when inserted into the host cell, causes morphological cell changes, loss of the gastric epithelial cell polarity, and resistance to apoptosis [36]. These bacteria may also inject a specific H. Pylori peptidoglycan into the gastric host cells which leads to stimulation and activation of the PI3K/Akt signaling pathway. Activation of this pathway results in stimulation of metastasis by interrupting the E-cadherin receptor to β-catenin linkage at the cell membrane. This mediates the actin cytoskeleton and induces transcription of genes involved in gastric adenocarcinoma metaplasia [36]. Similarly, the introduction of CagA into host cells stimulates β- catenin activity through the Wnt signaling pathway. This over-expression of the Wnt signaling pathway, or a mutation in the gene encoding for one of its mediators such as the Adenomatous Polyposis Coli (APC), can result in increased activity of β-catenin and its target genes. Over 50% of gastric adenocarcinoma cases are characterized by over-expression of the Wnt signaling pathway or APC mutation. This demonstrates the role that metabolites of *H. Pylori* can have in gastric carcinogenesis [36].

Colorectal Cancer (CRC)

CRC is one of the most commonly diagnosed cancers to occur in both men and women. In CRC, polyps develop on the lining of the colon and/or rectum and begin to grow uncontrollably [39]. In addition, there is an increasing association between the microbiome and the development and treatment of CRC (Table 4). Deep rRNA sequencing was used with human CRC-patient samples to analyze the difference in microbiota of "on-tumor" locations [40]. An overpopulation of the typically-probiotic subclass *Coriobacteridae* was found on the "on-tumor" samples, with a corresponding lack of strains of the potentially pathogenic *Enterobacteriaceae*. These findings promote two theories which aim to explain this observed difference in microbiota composition "on-tumor" and "off-tumor". One theory is that the microenvironment of CRC is colonized by anti-tumorigenic bacteria to prevent rapid carcinogenesis. A second theory explains that the bacteria found in "on-tumor" sites secrete a compound called butyrate. This compound is often considered to be anti-CRC by stimulating cellular signaling pathways associated with an upregulation of apoptosis. However, it is possible that the apoptosis-regulating characteristics of butyrate are only effective in early tumorigenesis.

Thus, theory two suggests that butyrate is instead functioning as an energy source for later stage tumors and may also suppress the inflammatory response of the immune system [40]. As with all cancer-microbiome studies, there exists possible outside factors which may affect the microbiome and cancer development.

In another study supporting the microbiota's role in CRC, researchers found that infection of the colon by *Citrobacter rodentium* promotes CRC carcinogenesis in the APC^{min} murine model [41]. *C. rodentium* is a commonly occurring bacterium in the gastrointestinal tracts of laboratory mice. In fact, the epithelial cell hyperproliferation that it can lead to has been compared to that of Crohn's Disease and ulcerative colitis in humans. These diseases are linked to an increased risk of developing CRC. Although the mechanism of *C. rodentium* influence is not completely uncovered, it is known that *C. rodentium* causes attaching and effacing lesions in the colon.

It is becoming well-appreciated by the general-public that early detection and screening is an essential factor in beating CRC. Despite the ongoing push supporting early screening and less invasive screening methods, it is reported that over 30% of Americans fail to seek and/or receive proper and timely screening. Researchers are aware of this screening gap and recent studies have provided optimism for future improvements in CRC screening techniques. One study compared the constituents of the microbiomes of healthy patients versus those with colorectal carcinomas or adenomas. This study demonstrated a clear difference in gut microbiome constituents between these three groups, indicating that evaluation of the microbiome may be a direction for the improvement of CRC screening. Data of the bacterial differences collected from both healthy and cancerous patients were used to develop improved models for predicting the presence of an adenoma or carcinoma [42]. This shows the positive effect that the consideration of the microbiome can have on cancer screening and diagnostics.

Skin Cancer

Fervent efforts have been devoted to a preventative medicine approach to skin cancer. The integrity of the skin microbiome is well respected as a protective and preventative agent against opportunistic pathogens. However, the possibility of the microbiome protecting the host from skin cancer is a new prospective role (Table 5). Individual constituents of the skin microbiome have been identified as possible biomarkers for melanoma. One study identified discrepancies between the skin microbiomes of melanoma-bearing Libechov mini-pigs as compared with control pigs that did not develop cancer [43]. Pigs with skin microbiomes that had higher percentages of *Lactobacillus* and *Actinobacteria* genera were less likely to develop melanoma than those with microbiomes that had lower Lactobacillus and *Actinobacteria* content [43]. Comparatively, pigs

Bacterial Strains Associated with the Malignancy	Details of Roles in Development and/or Treatment
Lactobacillus and *Actinobacteria*	Pigs with microbiomes containing higher abundances of these bacteria were less likely to develop melanoma.
Fusobacterium, Trueperell, Staphylococcus, and *Streptococcus*	Pigs with microbiomes containing higher abundances of these bacteria were more likely to develop melanoma.
Staphylococcus epidermidis	Produces the nucleobase analog 6-HAP, which can inhibit DNA polymerase in *de novo* UV lightinduced neoplasia to prevent proliferation of many human tumor cell lines.
Actionobacteria	• High percentages of this bacterium in oral microbiomes is associated with improved outcomes for HNSCC patients. • Produces chemotherapeutic secondary metabolites which have been further developed as drugs.
Actinomyces	Inverse relationship has been observed between abundance of the bacteria in the oral microflora and the T-stage of HNSCC.
Faecalibacterium genus, the *Ruminococcacae*, and *Bifidobacterium longum*	Higher abundance in responders to anti- PD1 therapy.
Bacteroidales order, *Ruminococcus obeum* and *Roseburia intestinalis*	Higher abundance in non-responders to anti- PD1 therapy.
Akkermansia muciniphila	Was present and elevated in fecal samples from melanoma patients who responded well to treatment.

Table 5: Bacterial strains and their roles in skin cancer

with microbiome profiles containing *Fusobacterium* and *Trueperella* genera developed melanoma. These pigs also had high abundances of *Staphylococcus* and *Streptococcus* [43]. This is interesting due to the correlation between *Fuscobacterium* and other cancers, like CRC, in which it has been associated with the induction of inflammation, proliferation, and disease progression [44]. Conversely, commensal strains of *Staphylococcus epidermidis* have been found to produce 6-N-hydroxyaminopurine (6-HAP), which is an antiproliferative nucleobase analog [45]. 6-HAP can inhibit DNA polymerases in de novo UV light induced neoplasia, thus preventing proliferation of multiple human tumor cell lines [45].

The prevalence of specific genera in a cancer patients' microbiome could be indicative of potential therapeutic effects. Having a high percentage of *Actionobacteria* in the oral microbiomes of head and neck squamous cell carcinoma (HNSCC) patients has been associated with better outcomes [46]. An inverse relationship was observed between the abundance of *Actinomyces* in the oral microflora of 121 patients and the T-stage of HNSCC [46]. T-stage indicates the size and spread of the tumor into adjacent tissues. The increased abundance of *Actinobacteria* was correlated with decreased T-stage of the HNSCC and better outcomes. This may be the case because many species of the *Actinobacteria phylum* produce secondary metabolites that have been developed into clinically-available chemotherapeutic drugs.

The role of the microbiome as a third immune system is still hypothetical. Stimulation of the immune system by the microbiome is associated with successful treatment outcomes of melanoma patients receiving immunotherapy. Surveillance studies have established a correlation between melanoma patient's progression of disease and the composition of their microbiomes. Studies have defined a correlation between increased diversity of oral and fecal samples and a higher response rate to anti-PD1 therapy [47]. Indicator organisms of the *Faecali bacterium* genus and the Ruminococcacae family were found in higher abundance in samples from patients who responded well to anti-PD1 therapy. Comparatively, an increased abundance of organisms of the Bacteroidales order were found in non-responder fecal samples [47]. Fecal microbiome transplant (FMT) is a prospective treatment for dysbiosis. To test this, genetically identical germ-free mice were given an FMT using malignant melanoma patient fecal samples. This was done to determine if the microbiome alone could influence effectiveness of PD-1 based immunotherapy in the murine models [48]. The samples came from both responder and non-responder melanoma patients undergoing anti-PD-1 therapy. The mice that received an FMT from responder patients had increased levels of cytotoxic CD8+ T cells. In contrast, the mice that received an FMT from non-responders had increased levels of immunosuppressive regulatory CD4+ T cells [48]. Moreover, individual bacterial species were significantly correlated with responsiveness to anti-PD-1 therapy, including *Bifidobacterium longum*. By comparison, *Ruminococcus obeum* and *Roseburia intestinalis* were correlated with non-responsiveness to anti-PD-1 immunotherapy [48]. These findings indicate the propensity for the microbiome to influence the host immune system. FMT is an emerging treatment for a variety of diseases, including Parkinson's Disease, Multiple Sclerosis, fibromyalgia, obesity, insulin resistance, and autism [49]. Collectively, there is evidence that FMT may also be a strategy for the treatment of cancer.

In another study of melanoma patient fecal samples, the presence of *Akkermansia muciniphila* was elevated in responder patient samples versus those of non-responders [50]. This study also explored the effect of antibiotics in combination with anti-PD1 therapy on the responsiveness to therapy. Antibiotic use corresponded with decreased responsiveness, possibly due to the induction of dysbiosis [50]. Compromising the diversity of the microbiome impeded the efficacy of immunotherapy. These findings are also supported by separate studies that have correlated intrinsic low-diversity and non-responsiveness to treatment [47,48].

Conclusions

Dysbiosis is a common denominator between leukemia, breast, skin, foregut, and other cancers. It can systemically and locally effect the progression and treatment of cancer. More so, modifying and monitoring dysbiosis could increase the efficacy of cancer treatment. Alternative approaches to cancer treatment include microbiomic profiling for risk stratification before antibiotic administration, probiotics, prebiotics, and fecal microbiome transplants. Unfortunately, despite the evidence correlating dysbiosis with cancer, robust clinical trials have not progressed to enhance cancer treatment using microbiome modification. In contrast, algorithms have been designed to predictively model cancer risk based upon genomic mutations [51]. With the amount of data that is being accrued regarding dysbiosis and the role of microbiome in cancer, similar predictive modeling could be employed. Lastly, cancer therapeutics are constantly being developed from the microbiome [52], including immunotherapy modulators and anti-tumor bacterial secondary metabolites. Altogether, this highlights the important role of the microbiome in the future of personalized medicine and cancer

treatment.

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