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Microbiome Signatures in Cancer Immunotherapy

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ABSTRACT

Cancer immunotherapy has transformed oncology, yet clinical outcomes remain highly variable among patients. Emerging evidence highlights the microbiome as a critical determinant of therapeutic efficacy and toxicity. Microbial communities influence tumor progression, immune surveillance, and the effectiveness of treatments such as immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T-cell therapy. Specific microbiome signatures characterized by enhanced diversity, enrichment of commensal taxa, and metabolite-mediated immunomodulation correlate with improved responses, whereas dysbiosis and reduced diversity are linked to resistance and adverse events. Immunotherapy itself also reshapes microbial ecosystems, underscoring a bidirectional relationship. Strategies to modulate the microbiome, including probiotics, prebiotics, dietary interventions, and fecal microbiota transplantation (FMT), have shown promise in preclinical and early clinical studies, with several trials demonstrating improved outcomes in refractory cancers. Despite encouraging findings, challenges remain, including methodological variability, reproducibility, and ethical considerations regarding microbiome interventions. Advances in metagenomics, multi-omics integration, and machine learning are accelerating the identification of predictive microbiome biomarkers, opening opportunities for microbiome-guided patient stratification and personalized immunotherapy. Harnessing microbiome signatures could thus optimize cancer treatment, reduce toxicity, and enable a new era of precision oncology.

Keywords: Cancer immunotherapy**,** Microbiome signatures**,** Immune checkpoint inhibitors**,** CAR T-cell therapy**,** and fecal microbiota transplantation.

INTRODUCTION

The remarkable success of immunotherapy in the treatment of a variety of cancers has revolutionized oncology and spawned numerous research efforts aimed at expanding the scope of this transformative approach. Yet, despite its widespread application as a promising treatment option, the variation in individual response to immunotherapy and the challenges in translating preclinical results to clinical practice remain significant hurdles. A rapidly growing number of studies from both human and mouse models have demonstrated commensal organisms inhabiting the host (also called the microbiota) to be an influential and partially addressable factor shaping immunotherapy outcomes, offering a variety of new strategies to be evaluated. Within the context of a cancer diagnosis, a healthy and diverse microbial community inhabiting the local tumor environment prevents disease progression and contributes to an improved survival rate [1]. The microbiota also influences tumor evolution through modulation of the immune response in ways that can be partially mimicked or enhanced by specific therapeutic interventions. A clear understanding of microbiome–immunotherapy interactions will thus be crucial for the further development of cancer treatment strategies and for refining efforts to develop microbiome-based diagnostics and prognostic biomarkers [2]. In addition, the mechanistic insights emerging from ongoing preclinical studies form a critical basis for the purposeful design of clinical trials geared toward microbiome modulation. This section establishes the broader clinical context with an overview of both the microbiome and cancer immunotherapy. The focus then narrows to the direct influence of the microbiome on the development and progression of the disease, followed by an in-depth discussion of the mechanisms through which microbiome signatures shape clinical response to immunotherapy, including opportunities for microbiome modulation. The review concludes by outlining recent advances and ongoing efforts to identify clinically actionable microbiome-based signatures.

Understanding the Microbiome

The microbiome encapsulates the collective genomes of microorganisms inhabiting the human body and the surrounding environmental conditions [2]. It encompasses immensely diverse and dynamic populations of bacteria, fungi, archaea, viruses, and other microorganisms that influence fluctuations in overall microbial composition and functions. Much of the human microbiota is composed of bacterial cells, with their physiological, genetic, and evolutionary characteristics determining their functions in the body. Characterizing the compositional variation of the microbiota thus remains a fundamental task for understanding human health states and diseases [2].

Definition and Composition

A microbiome is the entirety of microorganisms and their genes in a particular ecosystem, including bacteria, archaea, fungi, algae, and small protists. Microorganisms colonize the human body from birth onward [1]. Together with the host, the microbial community forms a holobiont, in which alterations in microbial genomes, abundances, or gene expression influence the expression of the host's genes. As such, the microbiome is considered a second set of human genes that regulates biological functions such as digestion, immune response, and aging. The genomic content of the microbiome is much larger than that of the host. Genome sizes of microorganisms range between a few hundred thousand and approximately 14 million bases, whereas the human genome comprises about 3 billion bases [1]. The human microbiome consists of 100 trillion microorganisms, on the order of ten times more than the number of human genes. Understanding the human microbiome is therefore crucial for the prevention and treatment of diseases and remains at the frontier of biomedical research [1].

Role in Human Health

The term "microbiome" denotes the ecological community of commensal, symbiotic, and pathogenic microorganisms found in or on the human body, with a collective genome vastly surpassing that of humans themselves. Characterization of microbiomes via 16S ribosomal RNA gene or metagenomic sequencing has unveiled the crucial role that these microorganisms play in human health and disease [3]. High variability across body sites means that specimens such as saliva, skin, stool, and vaginal secretions can be sources for monitoring individual microbiomes. Ecological shifts in microbial composition are associated with susceptibility to various conditions, including diabetes, autism, asthma, multiple sclerosis, and cancer [4]. In fact, the microbiome's role in immunomodulation can determine whether the host immune response promotes or restrains tumor growth 2. On the other hand, both infectious and commensal microbes contribute pivotal metabolic functions and immune stimulation that protect the host against pathogenic challenges [3, 4].

Cancer Immunotherapy Overview

Immunotherapy employs the intrinsic ability of the immune system to recognize and destroy tumour cells as an approach for cancer treatment. Among cancer treatment approaches, immunotherapy has successfully evolved from empirical immunostimulation to efficiently and selectively induce an antitumour immune response in various cancer types [1]. However, the efficacy of immunotherapy is highly affected by immune checkpoints such as programmed cell death protein-1 (PD-1), PD-ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), as well as chemicals such as lactic acid that create an immunosuppressive tumour microenvironment. Immune checkpoint inhibitors, such as human immune checkpoint monoclonal antibodies, recover or prevent the immune escape mechanisms employed by cancer cells to restore immune cell activity and function. This approach has demonstrated promising clinical efficacy in various cancer types, such as melanoma, non-small-cell lung, kidney, and bladder cancer [1]. Chimeric antigen receptor (CAR) T-cell therapy has demonstrated efficacy in the treatment of haematologic cancers after long-term remission [1]. In this approach, autologous T cells are modified to express CARs with different generations of stimulatory domains containing single-chain variable fragments constructed from a tumour antigen-specific monoclonal antibody and T-cell signalling domains. CAR T cells are expanded ex vivo before enabling efficient tumour-cell targeting and tumour regression after the interaction of the single-chain variable fragment of CARs with the corresponding antigen[1].

Types of Immunotherapy

Cancer immunotherapy elicits antitumor responses through three main approaches: immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell therapy, and cytokines. ICIs are monoclonal antibodies that target inhibitory checkpoint molecules, including programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). CAR T-cell therapy involves modifying human T cells ex vivo with specific receptors, such as anti-CD19, to recognize and attack tumor cells [5]. Cytokine therapy utilizes immunostimulatory signaling proteins like interferons and interleukins to enhance immune responses. Despite the expansion of immunotherapy applications, a significant proportion of patients with metastatic and advanced cancers exhibit resistance, underscoring the need for a deeper understanding of mechanisms underlying variable therapeutic efficacy [5].

Mechanisms of Action

Immune checkpoint inhibitors (ICIs) block immune-inhibitory pathways, preventing tumor cells from evading immune detection and clearance. Microbiome signatures correlate with differential ICI responses in multiple cancer types [6]. Gut microbiome-induced anti-tumor CD8+ T cell infiltration enhances the efficacy of checkpoint blockade [7]. Chimeric antigen receptor (CAR) T-cell therapy involves engineering patient T cells to specifically recognize tumor cells [8]. Microbiome signatures predict response to CAR T-cell therapy. Cancer patients harbor microbiome signatures associated with reduced anti-tumor immune cell activity and enhanced inflammation, consistent with microbiome modulation of ICI and CAR T-cell therapy responses [8].

Microbiome and Cancer

The microbiome affects the tumor microenvironment and cancer development by modulating immune reactivity, activating cytotoxic T cells, modifying the tumor microenvironment, and altering the host's metabolic function [1]. The microbiome influences cancers such as melanoma, breast, renal cell, non-small cell lung, and colorectal cancers by regulating physiological cell death pathways and thereby impacting antitumor immunity and immunotherapy response [9].

Impact on Tumor Microenvironment

The bacteriome has emerged as a crucial player in the tumor microenvironment in oncology [10]. Commensal microbes profoundly influence health and disease, including cancer pathogenesis, progression, and therapy. These microorganisms shape the immune response and modulate the tumour microenvironment, which affects tumour biology and the clinical course of disease [11]. Tumour-associated microbiota impact cancer progression and treatment by shaping the local immune infiltrate through immunological and metabolic mechanisms. Intratumoural bacteria are enriched in specific tumour types and anticorrelate with pathways of immune destruction, while directly influencing cancer cells by regulating tumor cell stemness and inducing genotoxicity [10, 11].

Influence on Immune Response

The host immune system is a critical modulator of tumor progression and a primary target of cancer immunotherapy [2]. Evidence from preclinical studies has demonstrated that the commensal microbiota can influence the differentiation and activation of immune cells essential for anti-cancer immunity [4]. Innate immunity provides the body's first defense against invading pathogens, while adaptive immunity initiates a complementary, delayed response. Innate and adaptive immune responses are vital components of anti-tumor immunity, with T-cell-mediated cytotoxicity being the principal mechanism; the commensal microbiota modulates these defense mechanisms and impacts the efficacy of immune checkpoint inhibitors [11]. Tumor and commensal-microbial-associated molecular patterns are recognized by Toll-like receptors, leading to the activation of proinflammatory mediators, including NF-κB and Interferon Regulatory Factors; activation of these pathways in the tumor microenvironment has been found to influence the immune response to colon cancer.

Microbiome Signatures in Cancer Patients

Microbiome signatures indicate the specific characteristics of microbial communities inhabiting particular environments. These composite multi-omics features, unique to specific niches, have become invaluable in general health research [5]. The microbiome encompasses the community of living microorganisms and their corresponding microenvironment, including distinct microbial niches and metabolites, associated with humans [9]. It differs from the broader term microbiota, which refers to the genomes of all microorganisms residing within the human body rather than the prokaryotes themselves [9].

Diversity and Composition

Microbiome profiling across 16 cancer types exposes a striking disparity between tumor and matched normal microbial diversities. Normal tissue microbiomes consistently surpass those at tumor sites in the Shannon diversity index [4]. Tumor microbiome α-diversity shows a clear cancer-type dependency: non-tumor-associated cancers (NTACs) such as breast invasive carcinoma, colon carcinoma, and squamous cell lung carcinoma exhibit higher α-diversity than tumor microenvironment-associated cancers (TMACs), including those of the liver, stomach, and pancreas [1]. In line with these observations, the grouping of NTAC and TMAC distinctly clusters tumor and normal tissue microbial α-diversities. While NSCLC exhibits a diversity pattern akin to TMACs, it closely clusters with NTACs [4, 1, 12].

Specific Signatures Associated with Cancer Types

Shared traits distinguish microbiome signatures that either contribute to effective cancer immunotherapy or relate to ineffective therapy or distinct cancer types[5]. Patients with immunotherapy-responsive tumors typically exhibit heightened community diversity and enrichment of commensal obligate anaerobes, whereas nonresponders show variable diversity and overrepresentation of Proteobacteria or other facultative anaerobes. Responses to PD-1 versus CTLA-4 blockade display overlapping signatures but differ from the profile observed in chimeric antigen receptor (CAR) T-cell therapy [5]. Beyond response stratification, microbiome signatures associated with specific

cancers have been identified, albeit with often limited quantitative overlap 6. Notably, samples from renal and cervical tumors resemble those from triple-negative breast cancer, while samples from melanoma, lymphoma, gastric, and colorectal tumors contain featured taxa distinct from those found in other cancers [5]. These observations suggest a close connection between the microbiome, cancer type, and immunotherapy response, which warrants further mechanistic investigation and offers potential pathways for microbiome-based patient stratification and therapeutic modulation [5].

Effects of Immunotherapy on the Microbiome

T-lymphocytes represent the final step in the antitumor response. They can be stimulated or reactivated either because the tumor cells themselves express antigens recognizable by T cells or because of cross-presentation of tumor antigens by antigen-presenting cells [1]. Microbiome signatures represent a promising noninvasive biomarker to monitor the dynamics of patients undergoing immunotherapy and guide treatment decisions [1]. Some immune checkpoint inhibitors influence the composition and functions of the intestinal microbiota. Anti-CTLA-4 reduces the density of intestinal microorganisms in nonresponding mice, increases it in responding mice, and concurrently modifies the relative abundance of bacterial taxa in the mouse model [1]. Microbiome profiles can also be altered following adoptive cell therapy (ACT) [4]. Adoptive cell transfer is an immunotherapy based on the reinfusion of autologous antitumor T lymphocytes. During all types of ACT (tumor-infiltrating lymphocytes, chimeric antigen receptor T-cell (CAR-T) therapy, T-cell receptor (TCR) gene therapy), the microbiome signature of patients strongly changes [1].

Changes Induced by Checkpoint Inhibitors

Checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1 biologics, have become critical tools for many cancer types. Evidence points to the gut microbiome as a contributing factor to patient responses [7]. Treatment with anti-CTLA-4 antibodies increases the abundance of Bacteroides species, which can promote Th1 immune responses; mice transplanted with B. fragilis treated with anti-CTLA-4 antibodies show better anti-tumour responses. A strain-resolved metagenomic investigation of 107 patients with rare cancers treated with an anti-PD-1 plus anti-CTLA-4 combination supports these observations, highlighting strains associated with improved progression-free survival and response [7, 12]. Related species include B. longum, and pathways linked to improved outcomes involve monosaccharide degradation, which may enhance epitope presentation [12]. In addition to therapy-induced changes, affected microbiome taxa modulate the tumour microenvironment. Antibiotic treatment prior to checkpoint blockade significantly worsens outcomes [12]. Moreover, the abundance of certain microbiota prior to treatment correlates with responsiveness; for anti-PD-1 therapy alone, microbiome profiles detected before treatment, rather than those after, provide better predictions of clinical response. A separate cohort of melanoma patients receiving anti-PD-1 therapy also confirms microbiome–outcome associations. Checkpoint inhibitors also influence the microbiota of organs outside the gut. Chimeric antigen receptor (CAR) T-cell therapy changes the oral microbiome, regardless of the initial diagnosis for autologous transplantation. Higher α-diversity and increased relative abundances of Actinomyces and Prevotella prior to treatment correspond with better prognosis, while lower α-diversity, increased Lactobacillus, and reduced butyrate- and propionate-producing bacteria associate with acute graft-versus-host disease [12].

Impact of CAR T-cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy is a type of adoptive T-cell therapy in which a patient's T-cells are genetically engineered to provide a T-cell receptor capable of targeting specific tumor antigens. Since 2017, the U.S. FDA has approved CAR T-cell therapy for selected recurrent and refractory haematological neoplasms. Encoding T-cells with antibody-like specificity enables a strong immune response even in the context of tumor-induced immunosuppression. Beyond the therapy's direct effects, therapeutic immune activation can shape the patient's microbiota, as microbiome-associated factors are also key for modulating host immune surveillance. Therefore, despite still being in early stages, the interaction between CAR T-cell therapy and the microbiome has started to be investigated[12]. Tan et al. found that increased relative abundance of Bifidobacterium longum and Leptotrichia amnionii in the oral microbiota is associated with complete remission after CAR-T-cell therapy. Zhang et al. identified several gut microbiota that can be used as non-invasive markers for predicting cytokine release syndrome in patients undergoing this treatment. Another study investigated fecal microbiota composition in patients receiving CD19-CAR T-cell therapy for large B-cell lymphoma, identifying associations between the microbiome and cytokine release syndrome as well as neurotoxicity [12]. In the context of acute lymphoblastic leukemia, Alhuraiji et al. found that patients with higher microbiota diversity before CAR-T-cell infusion were significantly more likely to achieve a response and maintained that microbiota diversity loss generally precedes bloodstream infections and antibiotic administration after the infusion [12].

Microbiome Modulation Strategies

Microbiome modulation strategies comprise approaches designed to modify microbial composition and functionality, with the goal of optimizing cancer immunotherapy outcomes through either enhancement of anti-

tumor immunity or mitigation of treatment-associated adverse effects. Common modalities encompass the administration of probiotics live microorganisms that confer beneficial effects; prebiotics, non-digestible substrates that selectively stimulate growth or activity of advantageous bacteria; synbiotics, combinations of probiotics and prebiotics; dietary interventions aiming to alter microbial ecosystems via nutrient-derived modifications; and fecal microbiota transplantation (FMT), involving the transfer of processed fecal matter from healthy donors to patients to restore microbial homeostasis [9]. Each modality presents distinct advantages and limitations. Probiotics offer ease of administration and potential supportive benefits but carry risks such as unwanted dissemination and horizontal gene transfer, and efficacy may vary based on strain composition and host factors, including HLA genotypes [2]. Prebiotics can target the commensal population without direct colonization but may be hydrolyzed before reaching the colon. Synbiotics combine these effects but require further clinical validation. Dietary interventions exert broad influences yet often demonstrate inconsistent outcomes due to individual variability. FMT has demonstrated superior efficacy in restoring high-diversity microbiomes correlated with favorable ICI responses; nonetheless, concerns persist regarding the transfer of pathogenic entities and the lack of standardised protocols, compounded by ethical, legal, and regulatory considerations. Alternative strategies under exploration include the utilization of nanotechnology for targeted microbial modulation, administration of bacterial metabolites such as short-chain fatty acids and inosine to influence immune homeostasis, antibody-mediated modulation to suppress immunosuppressive bacterial populations, phage therapy to target specific pathobionts, and live biotherapeutics with genetically engineered strains [9].

Probiotics and Prebiotics

Probiotics and prebiotics are dietary supplements commonly used to modulate gastrointestinal microbiota and have been shown to reverse disease-associated dysbiosis, improving patient health [9]. Probiotics confer health benefits by interacting with mucosa-associated lymphoid tissues (MALT) and can restore microbial homeostasis after perturbations caused by pathogens, stress, or disease. Several bacteria, including Bifidobacterium, Lactobacillus, and Enterococcus, have been proposed as probiotics, with Lactobacillus possessing antimicrobial, immunomodulatory, antiproliferative, antiangiogenic, and antimetastatic properties that benefit oncology patients. Prebiotics are low- or non-digestible food ingredients fermented by gut bacteria, selectively stimulating the growth and/or activity of beneficial bacteria in the colorectal tract, such as Bifidobacterium and Lactobacillus. Prebiotics also increase the production of short-chain fatty acids (SCFAs), which are vital energy sources for colonocytes, promote growth, downregulate intestinal inflammation and carcinogenesis, and reinforce gut barrier function. The combination of probiotic strains with prebiotics, known as synbiotics, enables enhanced probiotic growth and colonization in the digestive tract [9]. In cancer immunotherapy, probiotics and prebiotics influence the microbiome by increasing the diversity of immunometrically important microbial species associated with better clinical outcomes [13]. Despite encouraging effects on epithelial barrier integrity, immune response, and adiposity, some probiotic cocktails may delay microbiome restructuring and impair treatment sensitivity after antibiotic therapy before immunotherapy initiation. The specific strains administered, administration regimen, and host microbiome characteristics are pivotal factors for therapy outcome in immunotherapy [9]. Microbiome signatures in cancer immunotherapy patients often display a lack of certain probiotics or a compromised ability to maintain them, raising the question of whether such patients would benefit from enhanced probiotic support. Probiotic supplementation is emerging as an additional intervention to directly manipulate microbiome signatures and potentially improve immunotherapeutic efficacy [9, 13].

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) from healthy donors can restore microbial diversity in cancer patients, augmenting immunotherapy efficacy by boosting dendritic-cell and CD8+ T-cell infiltration. Clinical trials have linked progression-free survival and overall survival after immune checkpoint inhibitors (ICIs) to gut RL and specific taxa such as Faecalibacterium prausnitzii, Bifidobacterium longum, and Collinsella aerofaciens. Non-responders exhibit gut dysbiosis correlated with accumulation of Tregs and immunosuppressive myeloid-derived suppressor cells[15, 16]. Preclinical models demonstrate that gavage of responder stool into germ-free or antibiotic-treated mice enhances tumor control, supporting FMT as a strategy to modify the microbiome and potentiate anti-tumor immunity, notably in colorectal cancer [14]. Administration of healthy-donor stool by colonoscopy or oral capsules safely reprograms the tumoral microenvironment to an immunotherapy-sensitive state, correlating with increased microbial diversity and donor strain persistence in responders [15]. FMT also alleviates ICI-related colitis, further underscoring its role in optimizing the gut ecosystem to enable anticancer immunity [16].

Clinical Studies and Findings

Microbiome signatures have attracted broad interest as a correlating factor for immunotherapy outcomes and adverse events. Predicting clinical benefits and immune-related adverse events of immune checkpoint blockade therapy is crucial for many patients, yet current predictive models are inadequate. Analyses of 16S rRNA

sequencing and metagenome datasets have revealed some microbial markers with outstanding predictive power [5]. The prevailing hypothesis is that microbes can enhance patients' immune responses, thereby increasing sensitivity to chemotherapy and potentially improving the prognosis of patients with advanced non-small-cell lung cancer, as demonstrated by 16S and metagenomic data analyses. Microbial taxa and operational taxonomic units highlighted as important for predicting clinical benefit are largely consistent, even between immortalised databases and prospective cohorts, and many are also predictive of immune-related adverse events [5]. Thus, modelling immunotherapy outcomes based on microbiome data can potentially provide accurate prognostic and diagnostic information through machine learning, making clinical testing of such predictors a compelling prospect. Studies assessing the association of gut microbiome composition with checkpoint blockade outcomes and toxicity have yielded common features alongside unique microbial associations that may vary by indication and other factors [5, 17]. Concurrent antibiotic administration prior to treatment initiation with either programmed death (PD)-1 or programmed death ligand (PD-L) blockade appears almost universally associated with inferior outcomes, consistent with early observations of diminished progression-free and overall survival [17]. Randomised, controlled trials are comparing FMT to placebo; transfer of stool from responders alone can overcome resistance to PD-1 blockade in patients with refractory metastatic melanoma. The gut microbiome is increasingly recognised as an immunomodulatory factor in checkpoint blockade, with some microbial signatures correlating with toxicity development [5, 17].

Key Trials and Results

Monitoring studies have revealed that a gastrointestinal microbial signature is prognostic for progression-free survival in patients with rare cancers receiving immune checkpoint blockade [12]. When analyzing samples spanning multiple tumor types, the microbial signature remains a strong predictor of treatment response and clinical benefit at 12 months, outperforming species-level or clinical data alone[12]. Meta-analysis of additional cohorts supports that the microbiome signature is associated with favorable outcomes only if patients receive the same immune checkpoint blockade regimen. Benchmarking these strain-resolved microbial signatures across datasets confirms their broad relevance and suggests that microbiome diagnostics and therapeutics should be developed and tuned to the immune checkpoint blockade treatment rather than the underlying malignancy [12].

Correlations with Treatment Outcomes

Microbiome signatures are associated with clinical response to different cancer immunotherapy treatments [5]. Enrichment of bifidobacteria and metabolic pathways involving the biosynthesis of methanogenesis cofactors, such as folate, cobalamin, and ubiquinone, is observed in responders. When treating more than one cancer type simultaneously with cancer immunotherapy, intratumoural microbiome signatures of microbial diversity and composition correlate strongly with clinical response [6]. Microbial richness associates positively with overall survival in some cancer types, while microbial composition stratifies responders from non-responders and predicts progression-free interval in others. Microbiome diversity positively correlates with T- and B-cell-mediated immunity while remaining negatively associated with immunosuppressive networks. Microbial colonisation of tumour microenvironments is emblematic of tumour microbiome signatures and is likely indicative of better clinical outcomes across different immunotherapy regimens [6]. In responders to immunotherapy (including CTLA-4-antibody, PD-1/PDL-1-antibody, or CAR T-cell therapy), greater diversity of the bacterial microbiome is observed. Gut microbial species also associate with immunotherapy outcome; responders exhibit increased levels of Akkermansia muciniphila, Enterococcus hirae, Bifidobacterium pseudolongum, and Faecalibacterium prausnitzii and remain physically distinct from non-responders [6]. Gut microbiome composition also associates with treatment-related toxicities in patients treated with checkpoint blockade.

Challenges and Limitations

Microbiome signatures offer promising clinical guidance for cancer immunotherapy, delineating patients into distinct groups based on therapeutic response. Nonetheless, variability across studies complicates consensus. The standardization of microbiome research and comprehensive investigation of potential confounding factors are essential to overcoming these challenges [6]. Ethical considerations regarding the acquisition and utilization of patient fecal samples also constrain broader adoption of strategies such as fecal microbiota transplantation (FMT), suggesting that probiotics and prebiotics may serve as more practical alternatives. Addressing these issues remains a prerequisite for the clinical translation of microbiome signature-guided immunotherapies [6].

Variability in Microbiome Research

Over recent years, an increasing number of studies investigating commensal microbial composition on or within tumors or their surrounding tissue have sought to identify signatures or even taxa associated with a particular cancerous state or immune checkpoint blockade (ICB) response [5]. However, the impact of differences in methods, sample source, sequencing approach, and analytical approach may be greater than the underlying biology, frequently yielding contradictory conclusions or findings that fail to replicate due to the taking of shortcuts based on conventional wisdom rather than due diligence[5]. Identifying findings that can reliably be

replicated across cohorts involves careful consideration of the nature of analyzed samples (AUC: stomach cancer > NSCLC > renal cell carcinoma > urothelial carcinoma > squamous cell carcinoma). There is growing acceptance that many apparent results represent artifacts or false positives largely attributable to contamination arising from background sources (airborne, laboratory reagents, PCR amplification kits, extraction kits, etc.) [12]. The extreme sensitivity of polymerase-chain-reaction (PCR) amplification, which can retrieve a signal from a vanishingly minute number of template molecules, along with incomplete bioinformatics filtering, has led to a flourishing literature of misleading results and hazardous 'predatory citations'[5].

Ethical Considerations

The long–term ramifications of microbiome transmission have yet to be thoroughly explored, as they bear ethical implications partially reminiscent of those encountered in stem cell transplantation [12]. Early trials in melanoma report that fecal microbiota transplantation (FMT) from responders to immune checkpoint blockade led to clinical benefits in 30% of patients [18]. However, a growth-promoting gut bacterium offers an alternative hypothesis that raises questions about the desirability and safety of microbiome modulation strategies during cancer immunotherapy.

Future Directions

Exploring strategies to improve patient responses to immunotherapy is a vital area of research. Microbiome profiles already show promise as predictive biomarkers for treatment outcome and toxicity [1]. While the role of the microbiome in transplantation and graft-versus-host disease is well understood, preconditioning regimens for adoptive cell therapies typically do not consider the microbiome. Systematic analysis of graft, recipient, and environmental microbiomes using immunogenomic associations could provide a framework for such integration [17]. Clinical trials of microbiome modulation are underway; however, elevating this approach from investigational to standard requires systematic and standardized study of microbiome profiles and engagement with regulatory bodies. Incorporating microbiome analysis into therapeutic and diagnostic strategies promises accelerated benefits for cancer patients. The stage is set to broaden integration of microbiome profiles into personalized medicine and clinical practice [1, 17].

Personalized Medicine Approaches

Biomarkers predictive of clinical response to immune checkpoint blockade, the most widely used form of cancer immunotherapy, have proven elusive. Microbes inhabiting the distal gut accumulate genomic changes at an accelerated rate and thus have the potential to serve as sensitive biosensors of patient health [12, 17]. New experimental and computational methods allow interrogation of the gut microbiome at unprecedented strain resolution. Analysis of stool microbiome from diverse cancer patients enrolled in the LEAPS clinical trial of immune checkpoint blockade demonstrates that precise, strain-level microbial abundances are predictive of treatment outcome at the point of patient enrollment and can therefore serve as tumor-agnostic biomarkers [12, 17]. Moreover, these biomarkers exceed in predictive value and generalizability that of other hallmarks, including routine clinical information and higher taxonomic microbial abundances typically reported in prior studies. The corresponding collection of taxa that associate with positive clinical outcome reveals the critical importance of describing microbiomes at sub-species taxonomic resolution and the presence of highly predictive taxa common across today's most-used cancer checkpoint drugs [12]. Supervised machine-learning techniques demonstrate the diagnostic value of precise, strain-level quantifications of gut microbial abundance. Such information predictive of response or progression-free survival exceeds the value of routinely gathered clinical metadata or higher taxonomic rank abundances estimated by conventional methods [12]. External generalizability of the strain-level response signature across cancers and countries is established, both within the LEAPS clinical trial and in metastatic melanoma cohorts from other countries. Across cohorts, microbiome composition varies, likely influenced predominantly by differences in fecal collection and DNA extraction methods [12]. The approach contrasts with previous investigations by using strain-level signatures, contrasting anti-PD-1 monotherapy and combined anti-PD-1 plus anti-CTLA-4 regimes, by extending both the spectrum of cancers studied and the geographical span of the patient population. Cancer immunotherapy affects many of the main ecological determinants of the gut microbiome and can induce substantial and persistent changes in microbial composition. Confirmation of such effects across prevalent forms of immunotherapy reinforces the importance of addressing immunotherapy-induced alterations of the gut microbiome as a mainstay consideration during oncology treatment [12]. Enrichment with distinct microbial isolates used alone or in defined consortia, combined with or without checkpoint inhibitors, allows discrete and consistent modulation of the steady-state microbial composition and clinical outcome of checkpoint blockade therapy. Fecal microbiota transplantation, therefore, represents a highly versatile approach to shape microbiome signatures and potentially guide response to a broad spectrum of immuno-oncology treatments [12].

Integration of Microbiome Analysis in Clinical Practice

The microbiome is a key feature of human health and disease states owing to its involvement in developing the host's immune, digestive, and metabolic systems. Cancer immunotherapy is a promising approach to treating cancer that boosts the immune system's natural ability to fight cancer by accentuating immune responses against tumor cells. Microbiome signatures have been identified in various cancers [1]. A microbiome signature is a specific occurrence and quantity of microorganisms in a sample from a particular environment. Microbiome analysis can be integrated into clinical practice to influence surgical decisions, oncotherapeutic regimens, and approaches for combating resistance to immunotherapeutic agents such as those used in PD-1 and CTLA-4 blockade [1, 12]. Microbiomes exhibit wide-ranging effects on carcinogenesis, the tumor microenvironment, and therapy efficacy, which suggest that microbiome signatures can serve as potent biomarkers for monitoring and predicting treatment responses and patient survival. Microbiome profiles of cancer patients differ from those of healthy individuals. In most cancers, NRF2-related genes are suppressed when the associated microorganisms reach high abundance. Cancers with low microbiome diversity exhibit suppressed NRF2 signature genes and high microbiome abundance, with distinct microbiome signatures [1]. These findings indicate that microbial species have functional effects in the tumor microenvironment and interact with the immune response, warranting investigation as potential biomarkers or therapeutic targets [12].

CONCLUSION

The microbiome has emerged as a powerful modulator of cancer immunotherapy, shaping antitumor immunity, influencing the tumor microenvironment, and stratifying patient responses. Specific microbial signatures, including enrichment of taxa such as Akkermansia muciniphila, Faecalibacterium prausnitzii, and Bifidobacterium spp., correlate with improved outcomes, while dysbiosis is linked to resistance and treatment-related toxicity. Immunotherapy not only depends on but also alters microbial composition, highlighting a dynamic, bidirectional interaction. Modulation strategies ranging from probiotics and prebiotics to fecal microbiota transplantation and synthetic microbial consortia hold potential to enhance therapeutic efficacy and safety, although standardized protocols and regulatory frameworks remain urgently needed. Future directions include leveraging strain-level microbial biomarkers, integrating microbiome analysis into clinical workflows, and conducting well-designed, longitudinal clinical trials. By incorporating microbiome science into precision oncology, clinicians can advance toward personalized cancer therapies that optimize treatment response while minimizing adverse effects, ultimately transforming patient care.

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