



Bacterial Interactions and Cancer Prognosis: A Review of Their Role in Tumor Progression and Therapy

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Abstract:

The importance of the human microbiome in carcinogenesis, metastasis, and treatment response is being more and more demonstrated. Species of bacteria that have recently come to light as having a role in tumor biology and prognosis are summarized in this article. Metabolism changes, antitumor immunity is impaired, and chronic inflammation is promoted by microbial dysbiosis, according to cutting-edge molecular techniques like 16S rRNA sequencing and metagenomics. There is great potential for customized cancer care through therapeutic regulation of the microbiome, which might be achieved by the use of probiotics or fecal microbiota transplantation. Additionally, specific microbial signatures are becoming more recognized as biomarkers. The intricacy of microbial networks and inter-individual variability continue to hinder therapeutic translation, despite recent gains. To create proven diagnostic and treatment approaches based on the microbiome, ongoing multidisciplinary research is crucial.

Keywords: Microbiome, Cancer, Therapy, Tumor, Biomarkers.

التفاعلات البكتيرية وتشخيص السرطان: مراجعة لدورها في تطور الورم السرطاني

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الخلاصة:

تتضح أهمية الميكروبيوم البشري في التسرطن والانبات والاستجابة للعلاج بشكل متزايد. يتم في هذه المقالة تلخيص أنواع البكتيريا التي تم الكشف عنها مؤخرًا على أنها تلعب دورًا في بيولوجيا الأورام والتشخيص. وفقًا لأحدث التقنيات الجزيئية مثل تسلسل الحمض النووي الريبوزي ١٦S والميتاجينومكس، حيث تؤدي الاضطرابات الميكروبية إلى تغيرات في التمثيل الغذائي، وضعف المناعة المضادة للأورام، وتفاقم الالتهابات المزمنة. هناك إمكانات كبيرة لتقديم رعاية مخصصة لمرضى السرطان من خلال التنظيم العلاجي للميكروبيوم، والذي يمكن تحقيقه باستخدام البروبيوتيك أو زراعة الميكروبيوتا البرازية. فضلًا عن ذلك، أصبحت العلامات الميكروبية المحددة معترف بها بشكل متزايد كعلامات بيولوجية، ولا تزال تعقيدات الشبكات الميكروبية والتباين بين الأفراد تعوق الترجمة العلاجية، على الرغم من المكاسب التي تحققت مؤخرًا. ومن أجل وضع نهج تشخيصية وعلاجية مجربة تستند إلى الميكروبيوم، من الضروري إجراء أبحاث متعددة التخصصات بشكل مستمر.

الكلمات المفتاحية: الميكروبيوم، السرطان، العلاج، الورم، المؤشرات الحيوية.

1. Introduction:

More and more discoveries are elucidating the significance of the microbiome in shaping various traits, including health. Disruption in microbiota can influence normal biological functions and is thought to constitute the underlying etiology of various health problems. The role of commensal bacteria in cancer has recently gained attention [1]. Research shows that germs can affect the body in many ways, especially in relation to blood-related and solid organ cancers [2]. Tumor biology is shaped by the presence of bacteria either through their phenotypic characteristics or by the way tumor cells react to the presence of bacteria. To further complicate the relationship, research has also indicated that the development of cancer and its microenvironment can alter the local microbiome [3].

With advances in molecular diagnostics further characterizing the spectrum of bacteria and their characteristics, the implications of this stratification and how to apply that knowledge for prognosis are at the heart of research. The above evidence has led to a number of open questions on how several of these bacterial species could be serving as robust biomarkers to help in determining cancer prognosis [4]. This review delves into the various bacterial species that have been linked to cancer prognosis. It seeks to understand how these species contribute to tumor

progression and therapy response, and it emphasizes their potential as diagnostic and therapeutic targets in clinical oncology. The study is planned to be conducted according to the guidance. In conclusion, understanding the microbiome has generated both excitement and disbelief in cancer biology

2. The Microbiome and Cancer

The microbiome is increasingly associated with diverse diseases. In cancer, the bacteria and other microorganisms in the gut and body can affect the immune system and inflammation, both of which play a role in how cancer develops and how well treatments work. The gut contains many different types of microorganisms. Their variety is influenced by factors like food and antibiotics, but genetics plays the biggest role [5]. At the same time, the microbiome assists in digestion, host metabolism, and immune system regulation. A consequence of this is the strong influence that the gut microbiome can exert even on distant cells and organs located in the peripheral tissues. Moreover, several bacterial species, pathogens, or symbionts have proven to be potent modulators of tumor development, each through their mechanism of action [6].

Notably, there is both heterogeneity in the microbial composition and distinct roles of the microbiota in tumorigenesis, including mutual symbiosis and direct translocation from intestinal dysbiosis. Nevertheless, it is still not clear when bacteria extrinsically translocated from the dysbiotic intestine acquire a commensal phenotype by adapting to the specific milieu of the tumor microenvironment. By interacting with host immune receptors including Toll-like receptors (TLRs), bacteria can stimulate tumor formation. Binding to Toll-like receptors (TLRs) on immunological and epithelial cells, bacterial components called microbial-associated molecular patterns (MAMPs) induce inflammatory and signaling cascades, such as NF- κ B and STAT3. Chronic inflammation, DNA damage, and changes in the tumor microenvironment that promote cancer start and development are brought about by the persistent activation of these pathways. Moreover, these same patterns and antigens were shown to be expressed also by several different kinds of bacterial species; therefore, they can predict the degree of intratumor inflammation. The overall specificity about bacteria-induced cancer progression is due to the host's specific proteome as well as the transcriptional expression at the single-cell level, which at the same time is dependent on the single nucleotide polymorphisms that are present in the host's genome. At the same time, emerging evidence has implicated unique microbial dysbiosis in several different cancer types [7].

2.1. Role of the Microbiome in Cancer Development

Until recently, cancer was long thought of as a hereditary disorder originating from mutations that interfere with regular cellular regulatory systems. Cancer initiation and progression are shaped by a complex network of elements, including genetics, epigenetics, metabolism, the immune system, and microbes, according to current data. More and more data shows that external factors like immune cells, fibroblasts, blood vessel cells, nutrients, and other molecules from the surroundings are very important. Among these extrinsic factors, the microbiome is receiving much attention. The microbiome is now considered a major organ and consists of about 1 kg, half of microbial mass being in the colon, where the density is one of the highest on the planet, with a concentration of up to 10^{12} bacteria per gram of colonic content [8]. The microbiome has pleiotropic impacts in cancer through its metabolome. Microbial molecules can significantly influence several signaling pathways that change during tumor development, like NF- κ B, Wnt/ β -catenin, and various pathways related to cell death. Intriguingly, the microbiome has the ability to alter environmental compounds like PAHs through its metabolic processes. The production of reactive carcinogenic intermediates by some microbial transformations has the potential to facilitate the start of tumors. At another step of oncogenesis, the microbiome has been shown to incite inflammation, increased angiogenesis, and modified cell-mediated immunity, all of which result in tumor growth and heightened tumor vascularization [9]. With regard to pro-inflammatory properties of the microbiota, it is noteworthy that about 15 bacteria, either directly or indirectly, increase systemic inflammation. All of these organisms are Gram-negative bacteria, and some of them increase Toll-like receptors and secrete lipopolysaccharides, which contributes to inflammation that promotes tumorigenesis [10].

At the same time, the microbiome contributes to host defense, decreasing inflammation. Pathogenic bacteria produce small molecules interfering with tumor colonization. Most transcriptionally distinct genes dysregulated in cancer were enriched in functions controlling cell proliferation and death, migration, and cytoskeleton rearrangements. The processes affected by these genes complement what is already known regarding the criteria for tumor aggressiveness [11]. This suggests that interactors, through their metatranscriptome, represent a valuable source of diverse cancer development biomarkers. Recent results have highlighted the negative impact of antibiotics targeting the intratumoral pool of bacteria with a subsequent uncontrolled tumor progression. A strong link was found between higher levels of certain oral bacteria and lower chances of survival without disease progression in people with advanced

colorectal cancer [12]. Consequently, disruptions of the balance of oral flora seem to be a candid explanation for these observations. In a recent study, researchers have identified the strength of the oncological outcome by the oral flora, in particular, the tongue and the M5 site where certain germs were found to have an unfavorable outcome on survival. That is to say, unlike serum, mixed saliva partially depicts the systemic response and highlights the possibility of several future tumor sites being located in the upper gastrointestinal tract. Overall, these results provide a supplement to blood biomarkers allowing metastasis detection and suggest that measuring mouth saliva could improve cancer staging and anticipate progression/resistance [13].

2.2. Tumor Growth and the Role of Different Bacterial Species

Bacteria play an integral role in tumor growth dynamics. The introduction of harmful bacteria into animal models with tumors accelerates tumor progression, primarily due to chronic inflammation, cytokine production that promotes tumor growth, and suppression of the immune response. For example, mice infected with *Helicobacter hepaticus* develop liver and colon tumors through IL-6 and TNF- α pathways. Additionally, *Fusobacterium nucleatum* enhances colorectal cancer growth by affecting immune cell infiltration and β -catenin signaling, with tumors growing faster than in germ-free models, which demonstrate a significant decrease in tumor progression and metastases, emphasizing a role of bacteria in modulating the tumor microenvironment and thus having a direct impact on cancer progression. Few studies offer an experimental point of view on bacteria [14]. Bifidobacteria are a genus of anaerobic non-motile bacteria that are recognized for their ability to modulate immune checkpoints and are crucial for cancer immunotherapy response. However, they are commonly obtained through dietary changes and probiotic supplements, and a number of clinical trials have linked high levels to a better prognosis for breast cancer patients [15].

Experimental models have shown that certain species of *Pseudomonas*, notably *P. aeruginosa*, can emit cytotoxic chemicals and immune-stimulating molecules, which have anti-tumor properties. Antimicrobial substances produced by these bacteria inhibit the growth of competing germs; this finding has the potential to lessen the prevalence of antibiotic resistance in bacterial populations. In this case, the number of bacteria comes into play: at lower concentrations, other bacteria can reproduce faster than *Pseudomonas* and thus limit its actions. The interaction between gut bacteria, tumour growth, and the human immune system affects their overall dynamic [16]. A closed bacterial system delivered in a clinical model to patients was shown to not affect tumor progression in a trial. However, optimal therapeutic concentrations without compromising patient safety are a challenge, as clinical investigations

have demonstrated that bacterial levels achieved in vivo often remain below the cytotoxic threshold needed for effective tumor destruction, even at higher oral or intravenous doses. It is unclear whether potential pharmaceutical intervention or bacterial cocktails can only target cancer-related bacteria and optimize the healing process. Hence, it is of critical importance to investigate bacterial dynamic interactions in order to model and ultimately use them as effective interventions [17].

3. Methods of Studying Bacterial Species in Cancer Prognosis

Several sequencing-based methods have allowed detection and characterization of bacterial communities within tumor environments. Targeted sequencing approaches such as rRNA analysis have been used extensively to profile the microbial taxa present in cancerous lesions. While rRNA profiling methods do not allow for the resolution of bacteria at the species level and provide limited functional information, they can be useful for preliminary studies identifying microbiome differences in patient groups [18]. Importantly, using advanced genomic technologies, such as whole-genome shotgun sequencing, investigators can profile the diversity and abundance of all microorganisms within a given sample. More advanced methods employing host sequence depletion have also been described to afford even greater coverage of bacterial species present within a given context [19].

Animal models have become a more frequently utilized tool to study cancer-associated microbiota. Gnotobiotic animals, which are born and raised in germ-free conditions, can be colonized with known bacterial species of interest, providing interactions with the host and potentially driving other important pro- and antitumor phenotypes [20]. In order to model complex human environments, future studies should integrate a variety of methodological approaches from in vitro systems to in vivo animals to provide a holistic understanding. However, there are a number of limitations to utilizing animal models of bacterial interaction in cancer research, including microbiome differences in very different gut habitats between humans and traditional laboratory mice, as well as the reproducibility, interpretation, and translational potential of some previous results [21].

3.1. Sequencing Techniques

In the last few years, several technological advances have revolutionized microbiome or metagenomic studies. Among the most powerful techniques, the 16S rRNA gene is currently the most widely utilized molecular marker to estimate both the composition and the diversity of the associated bacterial communities. In contrast, whole-genome sequencing can quantify

differences in function, gene content, and genomic potential of the observed microbial taxa [22]. The main advantages of using high-throughput sequencing for microbiome analysis are its sensitivity, ability to explore the composition and genetic diversity of bacterial populations, and capacity to reveal the complex molecular processes in which bacteria are involved. With the use of reliable bioinformatics pipelines, taxonomic profiling and functional predictions are achievable, potentially leading to the identification of possible biomarkers for cancer prognosis [23].

The extensive use of high-throughput sequencing has revolutionized microbiome analysis in clinical practice, as well as in exposure research. Several challenges exist, however, when determining the taxonomic composition of bacterial communities by comparing sequencing data alone, including contamination and amplification of synthetic oligonucleotides. Moreover, the potential for error underlying next-generation sequencing should be clearly stated. When applying high-throughput sequencing analyses to investigate the role of bacterial communities as possible early predictors of cancer, a complex interpretation process is essential, which reflects the rate of turnover of the microbial population based on changes in its host's biology. Currently, although pilot studies have been performed, results from high-throughput sequencing have not been applied to cancer prognosis [24].

3.2. Animal Models

Animal models allow investigation of the interactions between bacteria and cancer under controlled conditions. Numerous different animal models exist, including germ-free mice, which are devoid of all microorganisms, and gnotobiotic mice, which can be colonized with unique bacterial communities. Gnotobiotic and germ-free models have been extensively used in order to understand the influences of the microbiome on host physiology [25]. From the study of microbiota composition to functional properties and mechanisms, animal models are directly related to the recruitment of experimental conditions to implications that mimic naturally occurring human scenarios. It is important to note, however, the limitations of these models, because of variations in immunological function, tumor biology, microbiome makeup, and metabolic responses between species, there is a certain amount of uncertainty and danger when results from animal models are applied to human cancer. Because of these differences, as well as the factors discussed in Section 3.1, results in humans may vary greatly from those in preclinical animal studies [26].

It is paramount that observations at the murine level can be validated with evidence in human data because the development and clinical innovation of bacterial therapies would be targeted at human cancer. Recent announcements of interest in sequencing the tumor microbiome in murine strains as a part of a Pre-Clinical Development Service program are a clear acknowledgment that animal models are still relevant in contemporary cancer microbiome research. Nonetheless, there are also practical and ethical considerations for extrapolating to human studies. The design of rodent trials, their potential mechanisms of action, and the regulation of trials that utilize bacteria as interventions are discussed in more detail in the following sections. Additionally, larger mammals can provide a good middle ground between murine and clinical research, though at greater expense, plus regulatory oversight and ethical considerations surrounding their use [27].

4. Clinical Implications of Bacterial Species in Cancer Prognosis

Understanding the role of certain bacterial species with clear oncogenic mechanisms in the context of cancer patient outcomes and treatment begins to directly meet clinicians' interests so that patients can be stratified into risk groups or exhaustively monitored high-risk patients, altering their prognosis by developing biomarkers. In addition, certain bacterial species with specific types of cancer predispose to certain types of prognosis, such as sepsis and other inflammatory diseases. Finally, evidence suggests that the patient's initial microbiome composition can predispose certain cancers to respond poorly to some therapies due to related mechanisms, offering possible therapeutic options. Based on that, patients showing changes in initial microbiome composition could be candidates for probiotic or antibiotic-tailored therapies that would also enhance treatment response, such as rebuilding the altered microbiome in autologous fecal microbiome transplantation [28].

The depletion or addition of commensal and non-commensal bacteria to the microbiome using antibiotics or pre- and probiotics to promote intense host-wide immune responses and alter immune memory could enhance treatment responses forthwith and maintain ongoing immunity to prevent repeated relapse for months or years. Possibly, cancer patients can begin several weeks or months before the administration of particular antitumor therapy with adjunctive treatments that first alter the immune repertoire. Particularly, the complex bacterial exposure history of myeloid-derived suppressor cells and tumor-associated macrophage immunosuppressive activities can be changed by the prescribed probiotics or targeted narrow-spectrum or combination antibiotics. In particular, the response to checkpoint therapy seems to be very quick when the treatment is given, offering an opportunity to attract those who will

treat it or to treat patients who respond to moderate and poor results, to those who become resistant after receiving immunotherapy for some time. It has been shown that certain bacterial species influence the immune response in cancer patients, especially those who have received radiotherapy and checkpoint inhibitors. It is crucial that all findings are validated in clinical trials to directly monitor and influence patient outcomes in oncologic clinical practice. More and more data shows that the human microbiome is important. We need to include microbiome research more in cancer care and research [29].

4.1. Therapeutic Opportunities

Although removing certain types of bacteria may have some bad effects on health, research shows that this can help cancer patients live longer. The recommendation is that specific antibacterials could be developed that could be administered in this capacity so that they do not contribute to or cause dysbiosis. Improved local delivery of already active compounds for cancer therapy by specific bacterial strains could be very interesting. Microbials are usually expected as adjuvant cancer treatment agents, and data have shown that they show little efficacy as a monotherapy [30]. Recombinant bacterial strains that can be a virulent, can be heterologously expressing certain genes, and could serve as a prospective novelty for future therapy may transform localized cancer into a tumor necrosis factor that derives a host immune response against non-targeted solid tumors. In addition to this local approach, based on TME targeting or adoptive cell therapy, multiple other engineered bacteria could also be given as a systemic approach to treat disseminated cancer. Interestingly, researchers have reported engineered Lp that have potential usage in the local treatment of carcinoma and melanoma. These enzymes could also be active in other solid tumors, such as liver cancer, which have developed immune escape mechanisms by increasing PD-L1 and TILT, another favorable aspect of Ovs (Figure 1). Sporadic reports have shown surprising results, such as Lactobacillus-based treatment showing better responses than PD-1 blockade alone in mice with melanoma and Listeria monocytogenes infecting brain tumors with fair prognosis, showing it as a novel method in glioblastoma treatment. Moreover, several clinical data make it possible to use bacteria that improve immunotherapy and chemotherapy responses, but this data is limited, and the use of bacteria to improve cancer responses is a part of an unknown field [31].

By using these strategies and information, harmful bacteria can be reduced in the gut that can lead to cancer, keep track of how the gut's bacteria change during cancer treatment, and tackle the real challenges of using gut bacteria to guide cancer treatment. Based on the latest findings, in this section, the recent studies on bacterial species and cancer have been described

that will be both effective methods to improve the responses of the bacteria to cancer and chemotherapy and methods that will be developed in the near future. It should be kept in mind that any bacteria could cause problems; also, reinforcement of one-way immune responses could bring successful responses in patients who have less possibility of response to immune checkpoints because of the composition of their personal microbiomes. Additionally, major challenges to bring these bacterial therapies to the clinic are reported in this section [32].

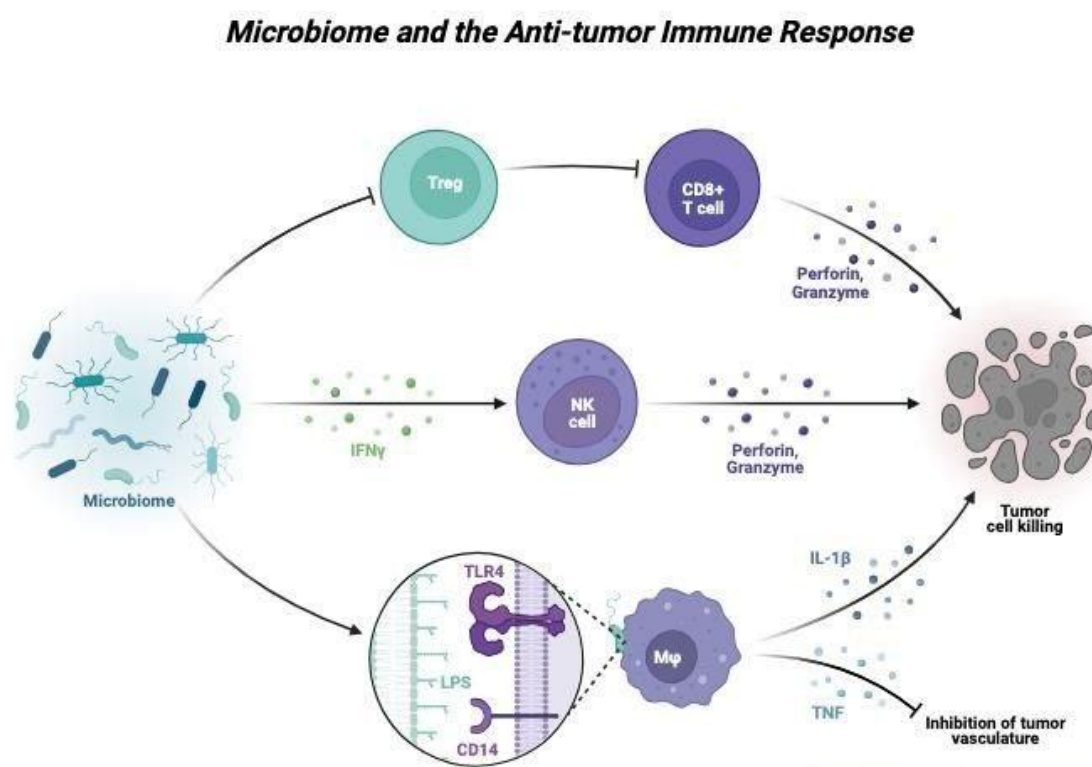


Figure 1. Proposed pathways linking the microbiome, immune modulation, and tumor progression.

4.2. Diagnostic Biomarkers

It is widely acknowledged that knowledge of the microbiome can help deliver biological meaning because some findings are related to changes in its composition, particularly to the increase of specific bacteria known as pathogens and vice versa. Many studies have found that

the makeup of gut bacteria changes in cancer patients, no matter what type of cancer they have. This has led some experts to think it could be used to help diagnose cancer. In fact, these shifts can distinguish neoplastic subjects from healthy individuals, allowing the research community to propose a new route for the development of non-invasive test technologies specifically for early cancer detection. Moreover, the microbial composition, considered as the "cancer microbiome signature," can distinguish among different types of neoplasms and is often linked to tumor progression features and host response [33]. These results support microbiome contribution due to host-tumor adaptation that is leading to a specific tumor immune detection and response. Additionally, this knowledge opens the door to new treatment approaches that target the microbiome to improve its ability to regulate immune recognition in the tumor microenvironment. To prevent immune evasion mechanisms acquired from tumors and restore immune surveillance, it may be feasible to influence the makeup and activity of microbes. Improving early cancer diagnosis through research into bacteria is driving idea that many emerging microbiome signatures are hoping to ultimately know as diagnostic markers. Indeed, many manuscripts have been published on this issue. However, in order to promote the clinical applicability of biomarkers, their interest and potential should be examined, meaning that they should be independently validated following an undisputed methodological design, compared to other validated markers and, if possible, subjected to laboratory standardization series across the different clinical levels and hospitals. In the case of bacterial signatures, this would involve sampling and analysis laboratories, technological platforms employed for the massive sequencing of the DNA, and bioinformatic pipelines and tools currently used for microbiota analysis [34].

The standardization of these techniques is necessary, especially for a predictive, preventive, and personalized medicine approach. However, moving the human healthcare cost-related microbiomics diagnosis towards an innovative approach would require changes at the hospital level. Furthermore, investment in technology and software platforms is necessary to keep the use of microbial patterns at a low cost, whether in research or therapeutic use. Many studies have been done recently on how certain germs in our bodies might help diagnose diseases, but not many of these findings have been used in hospitals or clinics. These have already led to the development of a color-based kit as a diagnostic marker, bacteria associated with liver disease relying on bile acids profiling, and the development of a predictive model of variations in the levels of some positive predictive markers in advanced fibrosis. Concerning the oncology field and the functional validation of selected species for therapy, trials are ongoing [35]. Therefore,

moving forward, significant gaps in the understanding of the mechanisms of action, pharmacokinetics/pharmacodynamics, and toxicity remain to be filled. The majority of microbiome research articles have suggested that modifications in the abundance of specific bacterial species are clearly associated with the presence of cancer. They might one day serve as the right source for developing a non-invasive diagnosis in cancer [32],[36]

5. Future Avenues of Research and Emerging Opportunities

As can be seen, there is enormous potential for future studies investigating the prognostic implications of microbial species in cancer prognosis. However, in order to achieve significant results in this field, an interdisciplinary approach is needed that binds the knowledge of microbiology and cancer research. Future large cohort studies could provide the much-advised power to further elucidate the complex dynamics and interactions between the microbiota and cancer. For this, a significant partnership will be needed between researchers, clinicians, and industry stakeholders. As a start, this approach will also have the potential to fill in the blanks of currently known and less known, usually recognized cancers' bacterial species [37]. Along with these subjects, there is a paucity of knowledge concerning the linkage that bacterial species may hold with rarer types of cancer, as there are no or very few studies about them. Because of this, all the possible ways that microbiota can affect cancer could be studied in order to have a more comprehensive picture. In addition to identification, longitudinal studies should also be undertaken to monitor changing trends of microbial composition over time through the carcinogenic process. In contrast to this speculation, it should also be assessed whether fecal, serum, or tissue bacterial species, when diagnosed, indicate a non-pathogenic composition and, therefore, are not harmonized with the pathological basis in the case of different types of cancer, which are known as confounding factors. Furthermore, because the gut-brain axis has a close relationship with cancer, the effect of the axis on the outcome of cancer is another noteworthy point [38]. Due to the paucity of research on the relationship between bacteria and general health, it is necessary to investigate the role of the microbiota in cancer outcomes[39].

6. Conclusions

The interaction between the human microbiome and cancer progression represents a critical frontier in oncology. Specific bacterial taxa influence tumor initiation, immune modulation, and treatment response, offering new opportunities for diagnostic and therapeutic innovation. Incorporating microbiome profiling into cancer care could enable personalized treatment selection and early detection of resistance. However, progress toward clinical translation requires methodological standardization, large-scale validation, and elucidation of causal

mechanisms. Future studies should focus on longitudinal and interventional designs to integrate microbiome-based diagnostics and therapeutics into precision oncology, ultimately improving patient outcomes.

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