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REVIEW ARTICLE

Microbial allies: Personalized probiotics and their role in tailoring cancer immunotherapies

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Abstract

The human microbiome plays a pivotal role in immune modulation, and its influence on the development and progression of cancer has gained increasing recognition. Based on the concept of cancer immunotherapy, personalized approaches are extensively explored to address the limitations and challenges associated with achieving optimal treatment outcomes. This review examines the emerging field of customized probiotics and their profound impact on tailoring cancer immunotherapies. It provides an overview of cancer immunotherapies, the intricate relationship between the microbiome and cancer, and the concept of dysbiosis in disease progression. By delving into the mechanisms through which probiotics modulate the microbiome, this review highlights the evidence supporting their potential application in treating cancer patients. The review also emphasizes the rationale behind personalized probiotics in cancer treatment, discussing strategies for tailoring probiotics to individual patients with case studies demonstrating their efficacy. In addition, it explores the underlying synergistic mechanisms between probiotics and immunotherapies, focusing on their effects on the tumor microenvironment and immune cell activity. Challenges and ethical considerations are addressed, including the potential risks associated with personalized probiotics, and future directions for research and clinical applications are proposed. Finally, the clinical implications and translational potential of integrating personalized probiotics into cancer treatment protocols are examined, emphasizing the need for standardized approaches and regulatory considerations. This review aims to provide a comprehensive understanding of the role of personalized probiotics in shaping the landscape of cancer immunotherapies, paving the way for innovative and tailored therapeutic interventions.

Keywords: Probiotic; Tumor; Cancer; Immunotherapy; Microbiome

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1. Introduction

The intricate interplay between the human microbiome and the immune system has unveiled a new frontier in the quest for personalized and effective cancer therapies. The microbiome represents the diverse community of microorganisms inhabiting the human body, which has a profound influence on health and disease.[1] The symbiotic relationship between the microbiome and the immune system is increasingly recognized

as a crucial determinant of the body's responses to various pathological conditions, including cancer.[2]

Cancer immunotherapies are currently heralded as groundbreaking treatments that harness the power of the immune system to recognize, target, and eliminate cancer cells.[3] Despite their success in some cases, the divergence of treatment responses and the diverse range of obstacles created by the tumor microenvironment have highlighted the need for more nuanced and personalized approaches that address the issues present in an individual's prognosis.[4] Recent advancements in understanding the role of the human microbiome have led to the exploration of personalized probiotics as potential allies in cancer immunotherapies.[5]

This review presents a thorough analysis of the burgeoning topic of altering probiotics and their influence on cancer immunotherapies. It begins by discussing the current cancer immunotherapeutic strategies and addressing the limitations that prompt the pursuit of specific therapeutic strategies.[6] Subsequently, this review explores the convoluted connection between the microbiome and cancer, emphasizing the role of dysbiosis in disease progression. It further investigates the mechanisms through which probiotics alter the microbiome, assessing the evidence supporting their integration into cancer treatment protocols.[7,8]

As the discussion progresses, the focus shifts to the rationale underpinning the use of specific probiotics in cancer therapy,[9] encompassing the customization of probiotics for individual patients and supported by case studies that illuminate the efficacy of such specified care. Uncovering the underlying mechanisms between probiotics and immunotherapies is a crucial aspect of our exploration, shedding light on how these microbial allies influence the tumor microenvironment and enhance immune cell activity.[10,11]

In addition, this review covers the difficulties and ethical considerations surrounding the use of customized probiotics in cancer treatment, providing a balanced perspective on the emerging drawbacks and benefits.[12,13] In conclusion, the review explores the clinical implications and translational potential of incorporating personalized probiotics into mainstream cancer therapies. This forward-looking analysis emphasizes the importance of standardized approaches and regulatory considerations related to the complex intersection of microbiology and cancer immunotherapy.[14,15]

Through this thorough investigation, this review aims to make a meaningful contribution to the evolving field of cancer treatment by paving the way for more specialized and effective therapeutic approaches tailored to the distinct microbiomes of individual patients.

2. Methodology

Comprehensive searches were conducted in electronic databases such as PubMed, Scopus, the Web of Science, and relevant scientific journals. The search terms included combinations of "personalized," "probiotic," "cancer," "immunotherapy," and related keywords. The search covered studies published up to August 31, 2023, to ensure the inclusion of the most recent research. Studies that focused on the relationship between probiotics, cancer, and immunotherapies were included. Primary research articles, reviews, and meta-analyses were considered, while non-English articles, conference abstracts, and studies with insufficient relevance were excluded. Relevant data were extracted from selected papers, including study design, participant characteristics, interventions (if applicable), key findings, and implications for the review's theme.

3. Cancer immunotherapies

The landscape of cancer treatment has been revolutionized by the advent of cancer immunotherapies, which harness the body's immune system to recognize and eliminate cancer cells.[16] Notable examples include immune checkpoint inhibitors, adoptive cell therapies, and cancer vaccines, each designed to enhance the immune response against tumors.[17] These therapies signify a paradigm shift from conventional treatments like chemotherapy and radiotherapy and have demonstrated remarkable success in specific cases.[18]

However, the efficacy of cancer immunotherapies is marred by significant limitations. Tumor heterogeneity poses a substantial barrier, with varying responses observed across different cancer types and even within individual patients.[19] In addition, the immunosuppressive tumor microenvironment can impede the effectiveness of immunotherapies, hindering immune cells from mounting a robust anticancer response.[20] Treatment-related toxicities and the development of resistance further underscore the need for more refined and targeted approaches.[21]

The inherent complexities and challenges associated with cancer immunotherapies necessitate a shift toward distinctive treatment strategies.[22] Traditional one-size-fits-all approaches may not sufficiently address the diverse molecular and genetic topography of individual tumors, leading to variable treatment responses.[23] Precision medicine, reshaping treatments based on individual patient characteristics, is gaining prominence as a means to overcome these challenges and optimize therapeutic outcomes.[24] By examining the microbiome's role in cancer

and analyzing how probiotics can balance this microbial ecosystem, the objective is to overcome the limitations of the available immunotherapies and aid in the creation of more specific and efficient cancer treatment plans.

4. Microbiome and cancer

Mounting evidence highlights the profound influence of the human microbiome on the initiation and progression of cancer.[25] The microbiome, comprising diverse microbial communities residing in various anatomical niches, has been implicated in regulating key processes such as inflammation, metabolism, and DNA damage repair, all of which contribute to the complex process of cancer development.[26] The dysregulation of microbial communities has been linked to an elevated risk of certain cancer types, emphasizing the critical need to understand the microbiome-cancer interplay for therapeutic interventions.[27]

The link between the microbiome and the immune system plays a pivotal role in shaping the anticancer immune response.[28] Commensal microbes actively contribute to the development and maturation of immune cells, influencing their activation and function. Conversely, the immune system regulates the composition and activity of the microbiome, creating a dynamic and bidirectional interaction.[29] This crosstalk is vital for maintaining immune homeostasis and mounting effective antitumor responses.

Dysbiosis, characterized by an imbalance or disturbance in the composition of the microbiome, emerges as a critical factor in cancer advancement.[30] Alterations in microbial communities can lead to chronic inflammation, impaired immune surveillance, and changes in host metabolism—factors collectively fostering an environment conducive to tumorigenesis.[31] Various cancers have been associated with dysbiotic conditions, encouraging researchers to investigate how restoring microbial balance might alleviate cancer risk and enhance therapeutic outcomes.[32]

The exploration of these connections serves as the foundational basis for understanding the potential of personalized probiotics in cancer immunotherapies. By modulating the microbiome, probiotics may influence cancer development, impact the immune response to tumors, and address dysbiosis, providing a novel avenue for contemporary and effective cancer treatments.

5. Probiotics as modulators of the microbiome

Probiotics, defined as live microorganisms conferring health benefits when administered in adequate amounts, have gained considerable attention for their potential to shape the human microbiome.[33] Typically consisting of beneficial bacteria like *Lactobacillus* and *Bifidobacterium* species, probiotics have been extensively studied for their role in maintaining gut homeostasis and exerting systemic effects.[34] In the context of cancer immunotherapies, the introduction of probiotics represents a promising avenue for personalized methods, capitalizing on their ability to modulate the microbiome (Table 1).

Probiotics exert their effects on the microbiome through a multitude of mechanisms. They competitively exclude pathogenic microorganisms, preventing their colonization and maintaining a balanced microbial community.[35] In addition, probiotics can produce bioactive compounds such as short-chain fatty acids (SCFAs) that contribute to the overall health of the microbiome.[36]

Table 1. Probiotic-mediated modulation of the human microbiome

Probiotic strain	Observed effect	Mechanism of action	References
Lactobacillus rhamnosus GG	Enhances intestinal barrier function; reduces gut inflammation.	Increases expression of tight junction proteins; modulates immune response through interaction with gut epithelial cells and immune cells.	42
Bifidobacterium longum	Improves gut mucosal barrier function; reduces irritable bowel syndrome symptoms.	Enhances the integrity of the mucosal barrier; modulates gut-brain axis signaling; exhibits anti-inflammatory properties by generating short-chain fatty acids.	43
Saccharomyces boulardii	Prevents and treats various forms of diarrhea, including antibiotic-associated, *Clostridium difficile* infections, acute and persistent diarrhea.	Interferes with pathogen adhesion to the mucosa; stimulates sIgA production; enhances immune signaling pathways.	44
Lactobacillus plantarum MF1298 and *Lactobacillus salivarius* DC5	Improves gut barrier integrity; reduces gastrointestinal inflammation.	Stabilizes gut mucosal barrier; anti-inflammatory effects by modulating cytokine profiles; influences gut microbiota composition.	45
Bifidobacterium longum BB536	Enhances immune function; improves bowel regularity.	Stimulates the intestinal peristalsis, increases intestinal barrier function, and mitigates inflammation, promoting gut motility and healthy gut microbiota balance.	46

Immunomodulation is a crucial facet, as probiotics interact with the host's immune system, influencing the activity of immune cells and the release of cytokines.[37] Furthermore, probiotics may directly impact the composition of the gut microbiota by promoting the growth of beneficial bacteria and suppressing harmful ones.[38]

Mounting evidence suggests a potential role for probiotics in cancer treatment and prevention. Preclinical studies have demonstrated that certain probiotic species can inhibit the growth of tumor cells, induce apoptosis, and modulate the tumor microenvironment.[39] Clinical investigations have explored the use of probiotics to mitigate treatment-related side effects in cancer patients, such as radiation-induced diarrhea and chemotherapy-associated gastrointestinal symptoms.[40] Moreover, probiotics have shown promise in enhancing the efficacy of cancer immunotherapies by influencing the body's immune response and the tumor microenvironment.[41]

6. Personalized probiotics in cancer immunotherapy

The administration of personalized probiotics into cancer immunotherapy holds substantial promise, driven by a compelling rationale rooted in the diverse and individualized nature of the human microbiome.[47] The microbiome exhibits considerable interindividual variability, impacting treatment responses and outcomes.[48] Recognizing this variability, customized probiotics seek to overcome this diversity by customizing therapeutics to the unique microbiome of each patient, maximizing the therapeutic benefit of cancer immunotherapies.[49] The rationale stems from the potential to improve the microbiome to create a more favorable environment for anticancer immune responses.

Strategic considerations must be made when merging probiotics for particular patients to guarantee accuracy and effectiveness. The selection of the right strain of probiotics is a pivotal aspect, requiring an in-depth knowledge of the patient's baseline microbiome composition and the potential to influence specific pathways related to cancer immunity.[50] Precision in dosage and administration protocols is also critical, considering variations in patient responses and the ever-changing nature of the microbiome.[51] Combining with other treatment modalities and therapeutic agents may further enhance the beneficial effects of personalized probiotics in the context of cancer immunotherapy.[52]

An increasing number of case studies contribute to the growing body of evidence that highlights the efficacy of personalized probiotics in cancer immunotherapy (Table 2). These cases showcase the positive impact of specified probiotic medications on treatment outcomes and patient responses.[13] Particular instances of improved immunotherapy efficacy, reduced side effects, and enhanced overall well-being underscore the potential of personalized probiotics as valuable adjuncts to conventional cancer treatments.[53] These case studies provide valuable insights into the feasibility and success of individualized probiotic strategies in diverse cancer scenarios.

In summary, integrating personalized probiotics into cancer immunotherapy represents a groundbreaking approach to addressing the limitations associated with microbial variation. The rationale, strategies, and empirical evidence outlined in this review contribute to the evolving paradigm of precision medicine in cancer treatment, emphasizing the potential of microbial allies to augment the effectiveness of immunotherapies.

7. Mechanisms underlying the synergy between probiotics and immunotherapies

Probiotics work in concert with cancer immunotherapies to enhance their efficacy by modifying the tumor microenvironment and fostering an immune-supportive

Table 2. Personalized probiotics in cancer immunotherapy

Study	Personalized probiotic intervention	Key findings
Gopalakrishnan *et al.*[54]	Oral administration of personalized probiotics based on individual gut microbiota composition in combination with immune checkpoint inhibitors (ICIs) for cancer patients.	Improved response to ICIs; enhanced antitumor immunity; increased infiltration of cytotoxic T lymphocytes into tumors.
Najmi *et al.*[55]	Customized probiotic supplementation tailored to individual gut microbiota profiles in cancer patients receiving immunotherapy.	Modulation of gut microbiota composition; reduction in immune-related adverse events; improved response to immunotherapy.
Miller *et al.*[56]	Personalized fecal microbiota transplantation based on gut microbiota profiling in melanoma patients treated with anti-PD-1 therapy.	Alteration of gut microbiota; improved response to anti-PD-1 therapies; prolonged progression-free survival and overall survival.
Routy *et al.*[48]	Fecal microbiota transplantation from responder patients to non-responder cancer patients receiving ICIs.	Conversion of non-responders to responders; increased diversity of gut microbiota; enhanced antitumor immune response.

milieu against cancer[57] (Table 3). Through the production of SCFAs and other bioactive compounds, probiotics can mitigate inflammation, remodel the extracellular matrix, and influence angiogenesis.[58] This regulatory mechanism facilitates the creation of a less immunosuppressive environment, thereby allowing for improved infiltration and function of immune cells within the tumor microenvironment.[59] In addition, probiotics may influence the balance of pro-inflammatory and anti-inflammatory cytokines, further shaping the immune landscape to enhance the efficacy of immunotherapies.[60]

Probiotics play a pivotal role in enhancing the activity of immune cells, augmenting the overall antitumor immune response. Certain probiotic strains have been shown to stimulate the activity of natural killer cells, macrophages, and dendritic cells.[61] This heightened immune cell activity contributes to improved recognition and elimination of cancer cells. Furthermore, probiotics may enhance the cytotoxicity of T cells, promoting their antitumor effects and potentially overcoming the immunosuppressive mechanisms present in the tumor microenvironment.[62]

The immunomodulatory effects of probiotics vary depending on the strain, with certain strains exhibiting distinct capabilities to manipulate immune responses.[63] For example, *Bifidobacterium* and *Lactobacillus* strains have been identified for their potential to enhance antitumor immune responses.[64] These strains can influence the activation and differentiation of immune cells, such as T cells and antigen-presenting cells, contributing to an orchestrated and potentiated immune response against cancer cells.[65] Comprehending the distinct immunomodulatory attributes of probiotic strains is crucial in customizing therapies that align with the distinct requirements of individual patients and the features of their malignancies.

In summary, the mechanisms underlying the synergy between probiotics and immunotherapies are multifaceted, encompassing the modulation of the tumor microenvironment, enhancement of immune cell activity, and the strain-specific immunomodulatory effects of probiotics. These discoveries enable the development of specialized probiotic regimens that can be selectively combined with cancer immunotherapies to enhance treatment outcomes.

8. Challenges and future directions

8.1. Addressing the heterogeneity of the microbiome

The primary challenge in integrating custom probiotics into cancer immunotherapy lies in the unique polymorphism of the human microbiome.[69] The vast individual variation in microbial composition necessitates modified approaches that consider the unique microbiota of each patient. Overcoming this barrier requires in-depth characterization of the baseline microbiome and the development of strategies to dynamically adapt probiotics to the evolving microbial landscape during cancer treatment.[70] Advances in high-throughput sequencing technologies and computational analyses are pivotal for deciphering microbiome complexity and devising precision strategies that account for interindividual variations.[71]

8.2. Standardization of personalized probiotic approaches

Another critical hurdle is the standardization of designed probiotic approaches, which is necessary to ensure consistency and reproducibility across diverse patient demographics and clinical settings.[72] Establishing standard protocols for strain selection, dosage, and administration schedules is imperative for translating personalized probiotics

Table 3. Mechanisms of probiotic-mediated immunotherapies and cancer therapies

Probiotic therapy	Observed effect	Mechanism of action	References
Bifidobacterium in combination with PD-1 blockade	Enhances antitumor immune response; improves the efficacy of PD-1 blockade in cancer immunotherapy.	Augments activation and infiltration of cytotoxic T lymphocytes into tumors; promotes dendritic cell maturation and antigen presentation; modulates cytokine production.	39
Bifidobacterium fragilis in combination with CTLA-4 blockade	Augments immunostimulatory effects; enhances the efficacy of CTLA-4 blockade in cancer treatment.	Induces interleukin-12-dependent TH1 immune responses; activates various immunomodulatory and signaling pathways.	66
Lactobacillus spp. in combination with chemotherapy	Reduces chemotherapy-induced intestinal mucositis; mitigates adverse effects of chemotherapy.	Enhances gut barrier integrity, reduces inflammation, and modulates gut microbiota composition to maintain a healthier gut environment during chemotherapy.	67
Saccharomyces boulardii as an adjuvant therapy	Supports immune function; aids in the prevention of chemotherapy-induced diarrhea.	Enhances gut barrier function; inhibits adhesion of pathogens to intestinal mucosa; modulates inflammatory responses; may enhance the effectiveness of chemotherapy by minimizing side effects.	68

from research to clinical practice.[51] Rigorous clinical trials with well-defined endpoints are essential to validate the efficacy and safety of personalized probiotic applications. Systematized efforts will facilitate the comparison of results across studies, enable meta-analyses, and contribute to the development of evidence-based guidelines for personalized probiotics in cancer immunotherapy.[73]

8.3. Potential risks and ethical considerations

The integration of personalized probiotics into cancer immunotherapy introduces potential hazards along with ethical considerations that warrant scrutiny.[74] Due to their live nature, probiotics may carry fundamental risks, such as unintended immune-modulating effects or interactions with existing prescribed medications. Ethical concerns also surround issues of informed consent, patient autonomy, and the responsible use of newly evolved therapies.[75] Ensuring patient safety through rigorous preclinical testing and adherence to ethical standards is paramount. Clear communication with patients about the experimental nature of probiotics after customization and the possible uncertainties involved is essential to uphold ethical standards in clinical practice.[76]

8.4. Future directions

Tackling the abovementioned challenges requires an orchestrated endeavor from researchers, clinicians, and regulatory entities. Future directions should focus on the development of advanced technologies for microbiome analysis, allowing for real-time monitoring of microbial dynamics during cancer treatment.[77] Collaborative initiatives are needed to formulate consensus guidelines for individualized probiotic therapy, emphasizing transparency and repeatability in study design and reporting. In addition, ongoing surveillance and post-marketing studies are crucial for continually evaluating the long-term safety and efficacy of customized probiotics in diverse patient populations.[78]

In summary, while personalized probiotics hold great promise in cancer immunotherapies, their integration presents challenges related to microbiome disparity, consistency, and moral dilemmas. Overcoming these hurdles and advancing future directions will pave the way for the responsible and effective incorporation of these probiotics into mainstream cancer treatment.

9. Clinical implications and translational potential

9.1. Integration of personalized probiotics into cancer treatment protocols

The clinical implications of individualizing probiotics in cancer immunotherapies suggest a transformative significance in optimizing treatment outcomes. Integrating probiotic medications into cancer therapy regimens entails customizing them to each patient's specific microbiome to maximize the effectiveness of immunotherapies.[68] As research advances, clinical trials exploring the interaction between personalized probiotics and existing cancer treatments are essential for validating the safety and efficacy of these applications. This combination has the potential to address the deficiencies of available cancer treatments and enhance patient responses overall.

9.2. Regulatory considerations for personalized probiotics in cancer therapy

The clinical potential of personalized probiotics in cancer immunotherapy demands careful attention to regulatory considerations. Regulatory agencies need to create frameworks that take into account the customization and ever-changing nature of probiotic therapy choices.[69] This regulatory oversight involves establishing instructions for strain selection, dosage, and administration protocols, as well as defining safety parameters for clinical applications.[70] Collaborative efforts between researchers, clinicians, and regulatory agencies are essential to navigate the regulatory landscape and facilitate the responsible translation of personalized probiotics from research settings to routine clinical trials.

9.3. Future directions for research and clinical applications

Future directions in the research and clinical utility of personalized probiotics in cancer immunotherapy focus on several key areas. First, it is imperative to further investigate the molecular insights pertaining to probiotics modulation of the microbiome and its impact on anticancer immune responses.[79] Advancements in high-throughput sequencing technologies will facilitate comprehensive profiling of the microbiome, enabling more precise interventions.

Second, robust clinical trials are needed to generate rigorous evidence supporting the safety, efficacy, and clinical benefit of personalized probiotics in a range of cancer populations.[80,81] These trials should incorporate conventional methodologies, including microbiome analysis, to guarantee consistency and cross-study comparability.

Third, additional research should address long-term outcomes and any side effects associated with prolonged probiotic use in cancer patients. Monitoring microbial activity over extended periods will contribute to a thorough understanding of the sustained impact of personalized probiotics on the microbiome and overall patient well-being.[82]

In summary, the clinical implications and translational potential of personalized probiotics in cancer immunotherapy are promising avenues for improving treatment outcomes. Regulatory considerations, future research goals, and their inclusion into treatment regimens all contribute to the changing landscape of tailored probiotics as microbial allies in customizing cancer therapy.

10. Conclusion

In the ever-evolving landscape of cancer immunotherapy, the incorporation of altered probiotics emerges as a frontier with transformative potential. This review explores the detailed connection between cancer immunotherapies and microbial allies, with a particular emphasis on the idea of adjusted probiotics. The collective evidence underscores the promise of leveraging probiotics to enhance cancer treatments, optimize therapeutic responses, and address the challenges inherent in the heterogeneity of the human microbiome.

While navigating the complexities of the microbiome-cancer-immunity axis, the introduction of personalized probiotics into cancer treatment protocols stands out as a beacon of hope. The realization that the microbiome profoundly influences treatment outcomes opens new horizons for precision medicine. Considering that each patient's microbial community is unique, customizing probiotic therapies could completely revolutionize the way cancer patients are treated.

However, there are difficulties on this path. Cautions need to be considered due to the wide range of the microbiome, the requirement for standardized practices, regulatory issues, and ethical ramifications. A multidisciplinary approach is required for the investigation of developed probiotics, with researchers, physicians, and regulatory agencies cooperating to maximize the advantages while upholding the highest standards of ethics and patient safety.

Looking ahead, future research directions and clinical applications must embrace the imperative of advancing our mechanistic understanding, conducting robust clinical trials, and exploring the long-term implications of personalized probiotics in diverse cancer patients. The promise of microbial allies in cancer immunotherapy hinges on our ability to translate insights from the laboratory bench to the patient's bedside responsibly and effectively.

In conclusion, the paradigm of personalized probiotics in cancer immunotherapies signifies a frontier where the convergence of microbiome science and precision medicine holds unparalleled potential. The symbiotic relationship between microbial allies and cancer therapeutics entices us to reconsider and refine our strategies, with the ultimate goal of providing more effective, personalized, and holistic approaches to cancer treatment.

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