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Review

Application of Gut Microbiomes in The Diagnosis and Treatment of Cancer

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Abstract

In this study, the gut microbiome was closely related to human health. Changes in intestinal microbial composition promoted carcinogenesis and cancer development. Specific intestinal microorganisms and their metabolites regulated host physiological functions and tumor microenvironment and significantly affected the anti-tumor treatment response and its adverse effects. Gut microbiome-based strategies have shown promising prospects in the diagnosis and treatment of cancer, and many novel intestinal microbiological manipulation strategies have emerged. At the same time, there were many challenges in transforming intestinal microecology research into clinical practice.

Key words: Gut microbiome; tumor microbiome; tumor microenvironment; immunotherapy.

Introduction

The gut microbiome is the largest and most important microecosystem in the human body. Moreover, it is a key factor in activating and maintaining intestinal physiological functions and is closely related to infections, digestive tract diseases, cancers, and other diseases (1). With the promotion of the technology of second-generation sequencing,

sterile animal culture, and other technical methods, gut microbiome-related research appeared to have a "blowout" trend and transformed gradually into clinical practice. Specific intestinal microorganisms and their metabolites participated in the development of tumors and had an important impact on tumor treatment response and adverse events (1). This paper reviews the progress in the application of the gut microbiome in the diagnosis and treatment of cancers.

1. Gut microbiome and cancer

1.1 Gut microbiome and cancer

Carcinogenesis and the development of cancer are influenced by many factors, such as diet, environment, heredity, microbial exposure, and host immunity, accompanied by a series of different cellular and molecular changes. Studies have confirmed that the gut microbiome is closely related to the occurrence and development of cancer. It was found that the composition and diversity of intestinal flora in colorectal cancer patients were significantly changed. The number of Firmicutes decreased, and the number of Bacteroidetes increased compared with the healthy control group. Specific flora, such as Bacteroides fragilis and Clostridium nucleatus, were often enriched in colorectal cancer tissues (2). In addition, dysbiosis was also prevalent in hepatocellular carcinoma, cholangiocellular carcinoma, pancreatic cancer, breast cancer, and other tumors far away from the digestive tract.

The gut microbiome promotes tumor development through multiple mechanisms. Intestinal microorganisms produce reactive oxygen, activate tumor growth-promoting signaling pathways, induce gene methylation, directly or indirectly damage cell DNA stability, and promote tumor development. Studies on patients with familial adenomatous polyposis (FAP) had shown that the production of enterotoxin-induced DNA damage in epithelial cells and the activation of the Wnt signaling pathway by pks $^{+}$E. coli and Bacteroides fragilis played a key role in the development of hereditary colorectal cancer. Short-chain fatty acids (SCFAs), such as butyrate and propionic acid, were important metabolites of microorganisms, which played a key role in the pathophysiological process regulated by intestinal microorganisms. Studies (3) have shown that SCFAs inhibit cancer development by enhancing mucosal barrier integrity, inhibiting chronic inflammation, down-regulating key Wnt signaling pathways, and inhibiting cancer cell proliferation. At the same time, SCFAs are involved in the regulation of immune function.

The gut microbiome promotes immune escape of cancer cells and induces carcinogenesis by inducing local and systemic inflammation of intestinal mucosa and promoting the formation of inhibitory immune microenvironment. The gut microbiome also affects the infiltration of immune cells, such as Treg cells and Th17 cells, in the intestinal mucosa lamella propria, which increases cancer susceptibility. Furthermore, adaptive immunity plays a key role in the regulation of cancer susceptibility by intestinal microorganisms, and T cell exhaustion is its underlying mechanism (4).

1.2 Tumor microbiome and cancer

A study (5) investigated the microorganisms in human breast cancer, lung cancer, and other tumor tissues and found that there were unique bacterial

populations in different types of tumor tissues, as well as a significant correlation between cancers and specific microorganisms. Tumor microorganisms were an important part of the tumor microenvironment, and they interacted with cancer cells, immune cells, stromal cells, and other components of the microenvironment. Surprisingly, breast cancer tissues far from the digestive tract had the highest number and diversity of bacteria.

The discovery of the presence of bacteria and other microorganisms in cancer tissues overturned the traditional view of "sterility in tumors" and has attracted the attention of many scientists. Scientists are trying to understand the effects of these microbes on the tumor microenvironment and explore the effects on tumor growth by intervening tumor microbiomes. Riquelme et al (6) found that the tumor microbiota of advanced pancreatic cancer patients with long-term survival had a richer genetic diversity. Fecal microflora transplantation (FMT) from pancreatic cancer patients with different survival duration could regulate the changes of intestinal microflora and the tumor microenvironment in mice and affect cancer cell growth. This study provided experimental evidence for the influence of tumor microorganisms on host immune response and cancer biological behavior. The in-depth study of the interaction between tumor microorganisms and tumor microenvironment, and the understanding of their role in the mechanism of anti-tumor drug resistance therapy, provides new clues and ideas for the construction of novel anti-tumor treatment strategies.

2. Gut microbiome and cancer diagnosis

Intestinal microorganisms commonly exist in the digestive tract and are closely related to human health. Some scholars have established a new sequencing method to track intestinal microflora changes over an extended period (7). They found that most microbial strains remained stable for a long time. However, changes, such as weight loss, significantly affected intestinal microbial strain composition and diversity, suggesting that intestinal microbial changes could reflect intestinal function and host health status. This characteristic of intestinal microecological stability and responsiveness to physiological changes also suggests the potential of intestinal microbiological detection for tumor diagnosis, treatment, and prognosis.

Similarly, gut microbes have been shown to directly damage cellular DNA and induce gene mutations. Escherichia coli carries the "island gene sequence" of the pathogenic pks gene (2). The enzyme encoded by Escherichia coli synthesizes Eschericin, which can alkylate adenine residues and induce DNA double-strand break. Similar organs before and after exposure to pks+ Escherichia coli had significantly different gene mutation labels. The same mutation characteristics were detected in two separate human colorectal cancer genomes, suggesting that the mutation characteristics of colorectal cancer may originate from DNA damage directly induced by specific intestinal microorganisms (2). This unique carcinogenic mutation "fingerprint" has potential application value in colorectal cancer screening and early diagnosis.

3. Gut microbiome and cancer treatment

Intestinal microorganisms and their metabolites are involved in drug metabolism, chronic inflammation, and immune regulation and influence the efficacy and adverse event of chemotherapy, radiotherapy, immunotherapy, and other cancer therapies.

3.1 Gut microbiome and perioperative management of cancer

Intestinal flora promotes nutrient digestion and absorption, maintains the integrity of the intestinal barrier, and regulates gastrointestinal hormone secretion and host immune function. Studies have shown that the perioperative intervention of gastrointestinal surgery significantly changed the diversity and characteristics of the composition of intestinal flora and caused intestinal microecological disorders, which affected the postoperative gastrointestinal function recovery of patients and increased the risk of complications such as anastomotic fistula and postoperative infection. Significant changes in intestinal microbial composition were observed in all the studies after gastrointestinal surgery and most frequently within three months of surgery in a meta-analysis of 14 studies (8). Studies (9) have found that in the intestinal flora of patients with anastomotic leakage, the abundance of bacteria of Triclosan and Bacteroideae with mucinous degradation was higher, but the diversity of intestinal flora was lower. On the contrary, the abundance of some strains, such as Prevotella and Streptococcus, was negatively correlated with the incidence of anastomotic leakage. Postoperative local tumor recurrence increases the risk of distant metastasis and affects patient survival. Studies (10) have confirmed that bacterial microbiota is involved in the regulation of adaptive immune cells, and some symbiotic bacteria can transform into pathogenic bacteria, induce a local inflammatory response, change intestinal immune microenvironment, and promote tumor cell colonization and cancer recurrence.

Presently, the relationship between the gut microbiome and gastrointestinal surgery and the relevant studies on the gut microbiome reconstruction in the perioperative period have gradually attracted clinical attention. The application of probiotics and other reconstruction strategies based on the gut microbiome in the perioperative treatment of tumors has shown preliminary efficacy (11). This application can reduce the influence of perioperative treatment on the gut microbiome and steady-state preoperative intestinal flora and reduce the engraftment of pathogenic microorganisms. Moreover, the positive application of probiotics to promote the gut microbiome reconstruction, which can effectively reduce the occurrence of postoperative complications and promote tumor patients' postoperative recovery and improve the curative effect of surgery.

3.2 Gut microbiome and cancer chemotherapy

In the era of target therapy and immunotherapy, chemotherapy is still the "cornerstone" of cancer treatment. Drug resistance and non-selective "cytotoxicity" are crucial factors affecting treatment. Panebianco et al (12) summarized the interaction between 5-FU, gemcitabine, cyclophosphamide (CTX), and other chemotherapy drugs and the gut microbiome. They found that chemotherapeutic agents generally affect the composition and diversity

of intestinal microorganisms and are associated with host multisystem pathophysiological changes and adverse events of chemotherapy drugs. Loman et al (13) observed the synchronous changes of paclitaxel in mouse behavior, central and peripheral immune activation, colon histology, and bacterial community structure. The results showed that the composition of intestinal microorganisms and bacterial diversity of fecal organisms in the chemotherapy group were significantly changed, and the diversity was significantly reduced, which was related to the change of behavioral response, cognitive impairment, and fatigue caused by chemotherapy. Among them, the substantial increase of Ruminiclostridium was significantly correlated with the increase of microglia staining, which may play a key role in the "microbe-enter-brain" axis. Treatment strategies targeting the gut microbes may reduce damage to intestinal integrity and its adverse effects, known as "cognitive change after chemotherapy," including fatigue, weight loss, and cognitive impairment.

The effect of the microbial metabolism of drugs on therapeutic effects has been widely recognized, and the composition of the gut microbiome affects chemotherapeutic drug metabolism and biotransformation. The gut microbiomes have been shown to influence chemotherapeutic pharmacokinetics, anti-tumor activity, and adverse events in a variety of ways (1, 12, 14, 15). Studies (1, 12, 14) identified and found a highly metabolized intestinal flora containing higher levels of β-glucuronidase is capable of transforming the inactive SN-38G into the active SN-38, which increased the risk of adverse events of CPT-11. The inhibition of these enzymes could reduce CPT-11 adverse events. The analysis of the microbiological composition of patients can be used to predict the efficacy and adverse events of CPT-11 in the treatment of colorectal cancer. The cytotoxic target of CTX is DNA.

Studies(12, 15) have found that the gut microbiome contributes to the remodeling of the anti-tumor immune response, and the anti-tumor effect of CTX depends on the specific gut microbiome, which partly depends on its ability to stimulate the anti-tumor immune response. Further studies showed that CTX selectively induced some gram-positive bacteria to enter the secondary lymphoid organs, stimulated the production of specific Th17 cell subsets, and induced memory Th1 immune response. Of these, Enterococcus Haicellus, B. Haicellus, and Bacillus Inihominis were shown to be associated with the efficacy of CTX and were involved in the regulation of tumor immune surveillance.

It is worth noting that this chemical-immune synergistic effect of "bacteria combined with CTX" may be an important mechanism of chemotherapy combined with immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC), urothelial carcinoma, esophageal cancer, and other tumors that have shown higher efficacy than single ICI. In the era of immunotherapy, it may improve the efficacy of chemotherapy combined with immunotherapy by manipulating specific intestinal flora and regulating the tumor microenvironment and host immune response, which has enormous potential significance and is worthy of in-depth observation and research.

Specific intestinal flora could affect chemical drug metabolism, anti-tumor activity, and adverse reactions, which provide feasibility for the application of intestinal microecological modulators,

antibiotics, fecal microbiome transplants, and genetic-engineered bacteria to manipulate the gut microbiome and design chemical treatment strategies with an "enhancing effect and reducing toxicity" result.

In fact, the use of intestinal microbial regulators to regulate intestinal flora to improve the efficacy of chemical drugs and reduce adverse events has been gradually transformed into clinical practice and show preliminary efficacy (12). However, not all intestinal flora is beneficial to chemotherapy. On the contrary, some intestinal flora is closely related to chemotherapy resistance. Studies (16) have found that F. nucleatum, commonly found in the mouth, promotes drug resistance to chemotherapy in colorectal cancer. Among them, the TLR-4/MYD88 signaling pathway and specific microRNAs-activating autophagy pathway are the important mechanisms of F. nucleatum affecting the chemotherapy response of colorectal cancer. In-depth studies of specific flora and related pathways and mechanisms can provide valuable insights for the clinical management of tumor patients, help to increase the efficacy of chemotherapy, and improve the prognosis of patients.

3.3 Gut microbiome and cancer radiotherapy

Radiotherapy uses ionizing radiation to act directly on the DNA of cancer cells and induce cellular DNA damage. Moreover, it promotes the normalization of the cancer vascular system, induces a systemic inflammatory response, regulates systemic immune function, and induces the abscopal effect. This distant effect on non-irradiated cells reflects that radiotherapy can induce cancer-specific adaptive immune responses and promote the immunogenic death of cancer cells.

Radiotherapy substantially changed the intestinal microbial characteristics, which had significant individual differences. Studies (17) have shown that radiotherapy induces dysbiosis and changes in the gut microbiome composition. Among them, Bifidobacteria, Clostridium difficile, and Prausnitzii fecal bacteria decreased significantly, while the number of Enterobacteriaceae and Bacteroidetes increased. The gut microbiomes can also significantly affect the sensitivity of mice to radiotherapy (18). Dysbiosis of the gut microbiome makes intestinal mucosa more sensitive to ionizing radiation and inflammatory damage, which is partly related to IL-1 levels. In contrast, the minimum radiation dose required to induce death and radioactive intestinal damage in sterile mice was higher. The survival time of sterile mice was also significantly prolonged after receiving the lethal dose of whole-body irradiation, and they were more resistant to radiation enteritis caused by a lethal dose of irradiation. The expression of human angiogenin-like protein-4 (ANGPTL-4), a lipase protein inhibitor, gave sterile mice the ability to resist intestinal mucosal damage induced by whole-body irradiation.

Radiotherapy, particularly stereotactic body radiation therapy (SBRT), induces a cancer-specific immune response and produces a distant effect, significantly improves efficacy, and prolongates patient survival. Radiotherapy, combined with immunotherapy, has become an important mode of cancer therapy. Paulos et al (19) demonstrated that the gut microbiome improved the anti-tumor activity of whole-body irradiation in pretreated tumor-bearing mice for adoptive therapy with specific

$CD8^+$T cells. This enhanced immune system's ability to attack tumors may be related to LPS release, CD14/TLR-4 signaling pathway activation, and adaptive immunity promotion. On this basis, the team successfully constructed TLR-4 agonists to improve adoptive T cell immunotherapy responses. Studies by Paulos have shown that the gut microbiome influences the immunomodulatory effects of radiation therapy, which has important clinical significance for exploring the regulation of intestinal microorganisms to optimize tumor radiosensitive-combined therapy strategies.

Radiation injury is still a crucial factor limiting the application of radiotherapy. Considering that radiotherapy induces gut microbiome dysbiosis and increases the sensitivity of intestinal mucosal injury, Cui et al (18) observed that the reconstruction of the gut microbiome plays an important role in promoting intestinal mucosal repair and maintaining intestinal mucosal integrity by using the FMT strategy. The results showed that the FMT could alleviate the damage to bone marrow and intestinal mucosa and significantly improve the survival rate of irradiated mice. The combination of FMT and bone marrow transplantation (BMT) has more efficacy and is safer in the treatment of acute radiation injury. In fact, probiotics for the prevention and management of radiotherapy-induced mucosal injury have been studied in several randomized clinical trials and have shown preliminary efficacy.

3.4 Gut microbiome and cancer immunotherapy

Recently, immunotherapy has been successful in various tumors, and some patients have thus achieved a real sense of "cure" and long-term survival. Among them, ICI immunotherapy is the most widely used in clinical practice. However, most cancer patients showed resistance to these new drugs. At present, the mechanism of such a low response rate of immunotherapy is still unclear, and the potential mechanisms include low-frequency mutation, cancer heterogeneity, and the formation of an inhibitory tumor microenvironment (20). Studies have confirmed that gut microbiomes and their metabolites have important regulatory effects on intestinal and systemic immune systems. The cancer immunotherapy response depends on the diversity and composition of the gut microbiome. Dysbiosis of the gut microbiome and specific metabolic product changes lead to intestinal and systemic immune system disorders, induce the formation of an inhibitory tumor microenvironment, affect cancer immunotherapy response, and increase immune-related adverse effects (irAEs).

Wargo et al (20) have confirmed that specific intestinal microbial communities regulated the therapeutic efficacy of ICIs. They found that stool samples and oral swabs from patients receiving anti-programmed death-1 (PD-1) treatment for malignant melanoma had higher levels of clostridium and ruminococcus, which promote cytotoxic $CD8^+$T cell infiltration, and responded well to PD-1 antibody treatment. Conversely, Treg cells and Myeloid-derived suppressor cells (MDSCs) increased in the tumor microenvironment of patients with higher Bacteroidetes levels, and the treatment response was lower. Fecal microorganisms transplanted from patients who responded to anti-PD-1 treatment significantly increased the infiltration of immune cells in cancer-bearing mice, and cancer growth was effectively controlled after ICI treatment.

The use of antibiotics affects the gut microbiome, and the effects of anti-tumor therapy, especially immunotherapy, are of general concern. Several studies have observed that antibiotic use is not conducive to ICI anti-tumor therapy. A summary analysis of results from POLAR and OAK clinical studies (21) showed that the use of antibiotics shortened the PFS and OS of patients with NSCLC using programmed death-ligand 1 (PD-L1) inhibitor Atezolizumab. However, the impact of antibiotic use on ICIs treatment is still controversial. Pushalkar et al (7) found that microbial "clearance" could remodel the tumor microenvironment of pancreatic cancer, induce the reduction of MDSCs, promote the activation of $CD4^+$T cells and $CD8^+$T cells, and prevent the occurrence of precancerous lesions and invasive lesions. The removal of intra-tumoral bacteria can up-regulate the expression of PD-L1 and enhance the ICIs response. In addition, a retrospective clinical study (22) observed that the outcome of immunotherapy was independent of the use of antibiotics. Therefore, antibiotics may not be "adverse" or negative in anti-tumor therapy, and prospective clinical studies are still needed to evaluate the impact of an antibiotic application on the efficacy of immunotherapy. An in-depth exploration of the relationship between the gut microbiome, tumor microbiome, and tumor microenvironment will provide a new perspective for the basic research and clinical practice of immunotherapy.

Compared with traditional treatment, ICI treatment significantly reduces adverse reactions, but it is still bound to have irAEs, such as colitis, pneumonia, and heart injury, and a small number of patients will have extensive, severe, and even fatal adverse reactions. Studies (20) have confirmed that specific intestinal microorganisms are associated with ICI-induced irAEs. Wang's team (23) reported, for the first time, the successful application of fecal microbiome transplantation for treatment in patients with refractory immune-related colitis after receiving cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and PD-1 inhibitors. Further observation showed that transplantation of healthy intestinal microorganisms could rebuild the intestinal flora of patients and effectively inhibit excessive immune activation of the intestinal microenvironment. These studies also suggest that gut microbes are associated with adverse events to ICIs. Precise manipulation of gut microbiota can improve the efficacy of ICIs and help to manage the irAEs of ICI drugs.

Gut microbiomes influence the ICI response, but the mechanism remains to be clarified. Among them, intestinal microbial metabolites are the main mechanism of regulating host physiological functions. Studies (24) have observed whether specific metabolites affect the response of CTLA-4 inhibitor Ipilimumab in patients with malignant melanoma. They found that the concentration of SCFAs was negatively correlated with PFS and OS. In the mouse model, SCFAs significantly limited the "release" of Ipilimumab's inhibitory impact on the tumor microenvironment and inhibited the activation of immune cells. In conclusion, these studies further confirmed the important regulatory role of specific intestinal flora in the tumor microenvironment and its impact on immunotherapy response, demonstrating the feasibility and potential application value of the precise manipulation of

specific intestinal microorganisms and their metabolites in improving immunotherapy response.

New strategies for intestinal microbial manipulation

With the development of research on gut microbiomes, scientists have found that many physiological and pathological processes are related to specific strains of the gut microbiome. These specific strains produce active metabolite molecules and participate in regulation mainly through the synthesis and degradation of substrates. Therefore, manipulating specific strains of intestinal microorganisms and changing the level of specific metabolites may regulate the effects of the gut microbiome on the physiological functions of the host intestine and system.

FMT is a relatively mature method for the manipulation of the gut microbiome and has been successful in the study of clinical transformation. However, its wide application is limited by the uneven source and diverse biological functions of fecal microorganisms (23). Scientists are turning to techniques, such as genetic engineering, for more effective and precise manipulation of specific gut microbes. Phage is a viral microorganism that lives in the biological network of the organism and can kill bacteria. Some studies (25) have established the Gut Virome Database (GVD) and identified numerous unique virus groups in the human gut. Almost all of them are phages. They then used the phagocytosis characteristics of phages to try to establish a treatment strategy that can adjust the dysbiosis of the gut microbiome back to a healthy state. This targeted elimination of "harmful" bacteria based on phages may have new implications for anti-tumor therapy targeting the gut microbiome. Zheng (26) used the bacteria gathered in the cancer tissues as the natural carrier to target the tumor, constructed the nanometer photocatalyst to charge the bacteria to enhance its metabolic activity, and used the light-controlled bacterial metabolites to treat and inhibit cancer growth.

Compared with complicated gut microbiomes, the detection and manipulation of small molecular metabolites may be more simple, accurate, and effective. Mager et al (27) reported a novel immune pathway for microbial metabolites activated by immunotherapy. They identified and confirmed that the metabolite inosine of Bifidobacterium pseudolongum can activate T cells and enhance the anti-tumor effect. This specific signaling molecule may be developed and applied to improve the ICI response. One study (28) described inducible promoters to cleverly design a "dimmer switch" that responded to artificial chemicals that were lacking in mice. It helped to accurately track and change the expression and function of the live bacteria gene in the gut microbiome of mice in real time by adding this chemical to drinking water to conditionally induce the expression of specific genes in Bacteroides.

Conclusion

Presently, whether and how gut microbiome research can be better applied to the practice of tumor diagnosis and treatment face many challenges. First, the gut microbiome has significant heterogeneity and is affected by many factors such as diet, drug exposure, and regional differences.

Moreover, its constituent characteristics are not clear and defined. Second, the regulatory role of the gut microbiome in host immunity and inflammation and related mechanisms are far from clarified, and the relevant research results are mostly from experimental animal models. However, the "natural" differences of intestinal microbes between experimental animals and humans require a cautious attitude toward the clinical transformation of gut microbiome research. In addition, the absence of biomarkers and other technical factors also limited the application of the results to explain the relationship between human and intestinal flora. Further research will help deepen the understanding of the interaction between intestinal microecology and tumor and promote the application of intestinal microbial strategies in tumor diagnosis and treatment and their clinical transformation.

Abbreviations

ANGPTL-4, angiogenin-like protein-4; BMT, bone marrow transplantation; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; CTX, cyclophosphamide; FAP, familial adenomatous polyposis; FMT, Fecal microflora transplantation; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse effects; MDSCs, Myeloid-derived suppressor cells; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; SBRT, stereotactic body radiation therapy; SCFAs, Short-chain fatty acids.

Declarations

1) ***Consent to publication***

We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.

2) Ethical approval and consent to participants

Not applicable.

3) ***Disclosure of conflict of interests***

We declare that no conflict of interest exists.

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5) Availability of data and material

We declare that the data supporting the results reported in the article are available in the published article.

6) Authors' Contributions

JA, LS, SQ wrote the manuscript and XT helped to revise the manuscript. All the authors have read and approved the final manuscript.

7) ***Acknowledgement***

None

8) Authors' biography

None

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