Gut Microbes and Treatment of Cancer

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Abstract. The gut microbes act as a barrier to pathogens and play an important metabolic role. If the balance between gut microbiota and the human body is disrupted, it will cause a variety of diseases. The gut microbiota is a contributing factor to *cancer* development. Firstly, this paper describes the influence of gut microbiota on *cancer* development. Secondly, the role played by gut microbes in *Cancer* radiotherapy, chemotherapy, and immunotherapy, focusing on the relevance and research progress of gut microbes and *cancer* immunotherapy.

Keywords: Gut Microbes; Cancer; Immunotherapy.

1. Introduction

The intestinal tract is an important digestive and immune organ of the human body, and the gut microbiota consists of 1013 to 1014 species of microorganisms [1]. In 2005, Eckburg through metagenome studies that the gut microbes contain six dominant groups. Including firmicutes, bacteroidetes, proteobacteria actinobacteria, verrucomicrobia, and fusobacteria. The firmicutes and bacteroidetes are the main dominant groups[2]. In 2010, Nature published that the human gut microflora can be divided into bacteroides, prevotella, and ruminococcus.

When the gut microbes are out of balance, the function of the immune system is disturbed, resulting in disease. Several papers confirm the association of gut microbes with endocrine disorders such as diabetes [3] and cancer [4]. In the case of diabetes, for example, recent studies have analyzed the composition of the gut microbes of children with type I diabetes and found that the gut microbiota of children with type I diabetes decreased in bifidobacteria and bacteria that produce lactate and butyrate but that the number of bacteroides increased, suggesting that the pathogenesis of type I diabetes is related to changes in the distribution and structure of the gut microbiota [3]. In 2007, Cani found that lipopolysaccharides (LPS) produced by gram-negative intestinal bacteria induced a chronic systemic inflammatory response in mice, resulting in an increase in fasting blood glucose, body weight, and body fat content, suggesting a close relationship between gut microbes and the development of diabetes. [5] In addition, gut microbes are involved in the pathogenesis of autoimmune hepatitis, with enterocyte, microfold cells (M cells), goblet cells, eosinophilic cells, intraepithelial lymphocytes (LEL), and macrophages playing an important role in the intrinsic immunity of the gut. In addition, dysregulation of gut microbes can also produce short-chain fatty acids, the lipopolysaccharide (LPS), And the bacteria can also act as antigenic ligands, weakening the tight links in the intestinal mucosa and allowing endotoxins from the gut to be transported outside the gut and to the liver via the portal vein. Gut microbes play a very important role in the pathogenesis of many diseases.

2. Intestinal Flora and the Pathogenesis of Cancer

A growing body of literature suggests that gut microbes are associated with cancer and that dysbiosis of the gut microbes can affect the development of cancer including those near or distal to the gut. The main known oncogenic intestinal microorganisms include helicobacter pylori(H.pylori), escherichia coli(E.coli), and fusobacterium nucleatum(F. nucleatum).According to an analysis of the 2018 cancer incidence and mortality database, 810,000 of these cases were caused by H. pylori. H. pylori enters the gastric epithelium via the cytotoxin-associated gene A of the type IV secretion-mediated pathogen, a microorganism that induces gastric cancer. Chronic infection with H. pylori triggers multi-step carcinogenesis, from chronic gastritis, tissue atrophy, intestinal metaplasia, and benign tumors to cancer. In addition, peptostreptococcus, slackia exigua, and dialister pneumosintes

is also potential driver of gastric cancer. The article *Mutational signature inco lorectal cancer caused by genotoxic pks+ E. coli* found that the genome of genotoxic E. coli contains the gene cluster of clb that synthesize the genotoxic agent colibactin. Using colibactin produced by gut microbes injected into human intestinal stem cells cultured in vitro, researchers found that colibactin or pks+ E. coli can cause genetic damage that leads to the development of colorectal cancer [6], The article reveals that metabolites produced by gut microbes can directly cause genetic mutations that can lead to cancer. F.nucleatum produces a specific protein involved in the immune receptors of T cells and natural killer cells(NK) block the effects of immune cells on tumor cells. F. nucleatum stimulates anti-inflammatory bone marrow cells, damages NK and T cells, acts by activating TIGIT and CEACAM1 inhibitory receptors, and induces WNT/β-catenin regulator ANXA1 to form malignant tumors. The increase of bacteroides is carcinogenic and studies have demonstrated a further quantity of bacteroides and fusobacterium in patients with colorectal cancer compared to normal subjects. In addition, gut microorganisms may induce DNA damage in liver cells, hepatotoxicity, or reduced levels of immune cells during the conversion of primary bile acids to secondary bile acids, thus promoting the development of liver cancer. Gut microorganisms affect the treatment of breast cancer by influencing hormone metabolism and affecting estrogen in humans, and gut microorganisms can also influence the development of brain tumors through the brain-gut axis. The gut can contribute to the development of cancer through dysbiosis of the biota. [7] (As shown in Figure 1).

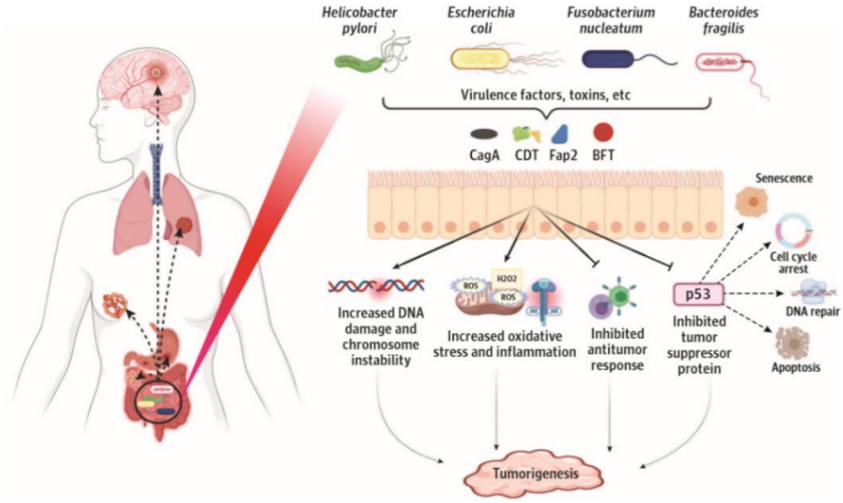

Fig 1. The impact of gut microbiota on cancer
Source: Liu L, Shah K. The Potential of the Gut Microbiome to Reshape the Cancer Therapy Paradigm: A Review. JAMA Oncol. Published online on April 28, 2022.

3. The Impact of Gut Microbes on Tumor Therapy

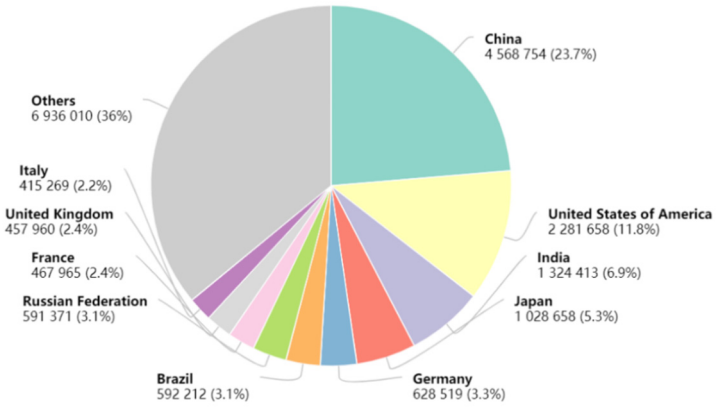

Fig 2. Global incidence of new cancers

The number of cancer deaths in China is 3 million in 2020. China ranks first in the world in the number of new cancer cases [8]. (Figure 2) Currently, surgical resection, radiation treatment, chemotherapy, targeted therapy, and immunotherapy are commonly used to prolong the survival of patients, depending on their condition. Studies have proven that the gut microbiota is involved in the process of chemotherapy, radiation treatment, and immunotherapy.

3.1 Gut Microbes and Radiation Treatment

Radiation treatment is a local treatment method that uses radiation to treat tumors and cancer.[9] Ionising radiation can have a direct and noticeable effect on the intestinal mucosa and microbial. The structure of the intestinal flora is also significantly altered when patients are treated with radiation treatment. Nam found that firmicutes decreased by 10% and clostridia increased by 3% after pelvic radiation therapy in patients with gynecologic tumors and a significant change in gut microbes [10]. The use of radiation treatment to treat pelvic and abdominal tumors can easily cause radiation damage to the gut, resulting in abdominal pain, diarrhea, increased stools, and mucopurulent stools. Therefore, monitoring and detecting gut microbe's instability, and making active adjustments and interventions will help to reduce the toxic effects of radiation treatment. In addition, gut microbes can also influence the therapeutic effect of radiation treatment. Gerassy-Vainberg found that germ-free mice survived longer after irradiation and that higher doses were required to induce germ-free mice to acquire enteropathy[11]. In some clinical studies, bifidobacterium, lactobacillus acidophilus, and lactobacillus casei have been shown to reduce diarrhea associated with radiation treatment [12]. Regulation of gut microbes may improve the sensitivity and prognosis of tumor radiotherapy.

3.2 Gut Microbes and Cancer Chemotherapy

An imbalance of gut microbes may affect the efficacy of chemotherapy. Among the drugs used in the treatment of patients with colorectal cancer, the 5-Fluorouracil(5-FU) has efficacy varies considerably between individuals and the differences may be related to the gut microbes between individuals. gut microbes can modulate the activity of some chemotherapeutic drugs through enzymatic biotransformation pathways, which in turn weakens the effect of chemotherapeutic drugs. Escherichia coli can enhance the cytotoxicity of CB-1954 through enzymatic modulation. Escherichia coli reduces the potency of Gemcitabine [13]. The gut microbiota alters a patient's sensitivity and response to chemotherapy through immune regulation. CTX is an alkylating chemotherapeutic agent that induces antitumor immunity by depleting immunosuppressive Treg and promoting cellular differentiation of helper T cells. CTX alters the gut microbes to enhance their immunomodulatory effects. [14].Oxaliplatin is an anti-tumor drug, Fusobacterium nucleatum not only does it lead to the development of rectal tumors, but it also induces resistance to chemotherapy with oxaliplatin and 5-FU. It activates the TLR-4/MYD88 dependent pathway and inhibits microRNA to convert CRC cells from apoptosis to autophagy, increasing the survival rate of CRC cells under chemotherapy. Oxaliplatin-induced anticancer immune responses require oxaliplatin-induced apoptosis and antigenicity of immunogenic intestinal symbionts. Immunogenic bacteria including NTBF and erysipelothrix. Immunogenic bacteria signal to TFH by stimulating migratory dendritic cells (DCs) with IL-1β and IL-12.Stimulated TFH cells interact with B cells to increase IgG2b responses and enhance antitumor effector/memory CD8+ T cell activity. However, these immune responses were significantly reduced in the absence of immunogenic intestinal symbionts. Intestinal commensal bacteria such as lactobacillus acidophilus also play an important role in the anticancer effects of cisplatin and Oxaliplatin, while the anticancer effects of cyclophosphamide are also dependent on Enterococcus hirae, Barnesiella intestinihominis [15].Thus, the gut microbes influence the course of chemotherapeutic effects and the overall outcome after treatment through direct or indirect modulation.

3.3 Gut Microbiology and Tumor Immunotherapy

Immunotherapy is the use of drugs or biological agents to regulate the immune status of the body so that the body produces an appropriate immune response to disease. Immune-checkpoint inhibitors are a transformative advance in cancer treatment. The successful development of immunotherapeutic agents such as PD-1, PD-L1 and CTLA-4 has been an important development in the field of oncology treatment in the past two years, and several studies have shown a correlation between gut microbes and immunotherapy efficacy.A team in Shanghai studied 37 patients with advanced non-small cell lung cancer who were treated with nivolumab. Stool samples were collected at baseline, at the time of treatment, at the time of efficacy assessment, and at the time of disease progression to determine microbiological characteristics by 16S (Microbial population identification sequencing) and peripheral blood was collected to determine peripheral blood immunological characteristics by flow cytometry. The results showed that patients with high microbial colony diversity had significantly longer PFS than those with low microbial colony diversity, and that patients with high microbial colony diversity produced more memory CD8+ T cells and NK cell subsets after immunotherapy[16].

In addition, gut microbes affect the efficacy of immune checkpoint inhibitors therapy. In germ-free mice, the anti-tumor effects of anti-CTLA-4 antibody treatment were eliminated, while in preclinical mouse models, the use of antibiotics to disrupt the gut microbiota reduced the efficacy of immune checkpoint inhibitors therapy. The introduction of Bifidobacterium and Bacteroides fragilis restored the therapeutic efficacy of anti-PD-L1 and anti-CTLA-4 antibody therapy in mice, demonstrating that Bifidobacterium and Bacteroides fragilis enhance the efficacy of CTLA-4 monoclonal antibodies. Zhou Cai's team finds that antibiotic treatment has an impact on the composition of the intestinal flora, which in turn has a negative impact on immunotherapy in advanced NSCLC[17]. It has been demonstrated that patients who have taken antibiotics and are treated with PD-1 inhibitors experience a rapid recurrence of cancer and a significant reduction in survival time and that disruptions in the body's gut microbes will also significantly reduce the effectiveness of PD-1 inhibitors. When feces from patients who respond well to immunotherapy are transplanted into germ-free mice, the therapeutic effect of the germ-free mice will be improved. This means that the right bacteria in the gut microbiota have an important impact on cancer immunotherapy.

Gut microbes as important predictors of immune checkpoint inhibitors therapy in melanoma patients. In 2017 Gopalakrishnan V used PD-1 monoclonal therapy for melanoma patients. The composition and diversity of the gut microbes differed significantly between the two groups of patients, which were divided into R (respond) and NR (non-response) according to their response to immunotherapy. The relative abundance of ruminococcus in patients in the NR and R groups were significantly different. Favorable microbiota in group R patients increases systemic anti-tumor immune function[18]. It is evident that gut microbes affect an individual's immunity to cancer and the individual's response to immunotherapeutic agents.

4. Summary

In summary, gut microbes are associated with tumor and cancer development, and influence the effectiveness of cancer immunotherapy. Gut microbes play a tumor-promoting or tumor-suppressing role and influence the efficacy and toxicity of cancer treatments. Beneficial gut microbes promote the antitumor activity of immunotherapeutic agents through immunomodulation. gut microbes are considered a potential biomarker to predict the efficacy of tumor immunotherapy. As a result, gut microbes are used as an effective way to treat and prevent cancer. However, knowledge of the specific functions of each gut microbe in cancer types is still limited. Currently, mouse models have been used to simulate human host-microbiota ecosystems. However, tumor cells transplanted into mice do not undergo multi-step tumorigenesis and do not interact closely with the microenvironment. In addition, tumor transplantation procedures can alter tumor characteristics and anti-tumor immunity, and differences in composition between human and mouse microbiota clearly confounded the results. Therefore, efforts should be made to develop host-microbiota ecosystems that realistically mimic

humans, to increase understanding of the cancer host-microbiota ecosystem, and to expand precision cancer treatment.

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