



Effect of Gut Microbiome on Chemotherapy Response in Patients with Colorectal Cancer: a Prospective Cohort Study

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Abstract: This review aims to explore the emerging role of the tumor microbiome in tumor development and treatment, particularly in the impact of chemotherapy responses in patients with colorectal cancer. We discussed that the gut microbiome may influence the occurrence and progression of colorectal cancer by participating in the occurrence of colorectal cancer and regulating the host's immune response and metabolic status, as well as the effect of chemotherapy by influencing drug metabolism, regulating immune response, or participating in the side effects of chemotherapy. Research suggests that tweaking the gut microbiome may help improve the efficacy of chemotherapy. This may involve strategies such as the use of probiotics, prebiotics, or fecal microbial transplants. However, there are many challenges to the application of these strategies, such as the fact that we do not yet know which microbes are beneficial and which are harmful, and that the same strategy may have different effects on different people. Future research may therefore focus on a deeper understanding of how the gut microbiome influences tumor biological behavior and how this knowledge can be used to improve treatment outcomes for patients with colorectal cancer.

Keywords: intestinal microbiome, colorectal cancer, chemotherapy, prospective cohort study

1. Introduction

In recent years, the development of microbiome research has revealed the important role of gut microbial communities in maintaining health and the occurrence of disease[1-2]. Among them, the relationship between intestinal microbiome and tumor has attracted more and more attention. The gut microbiome, the large and diverse community of microbes in the human body, has been shown to play a key role in the occurrence, development and treatment of many diseases, especially in the field of cancer[3-5].

Colorectal cancer is one of the tumor types with high morbidity and mortality in the world[6]. Despite significant advances in the treatment of colorectal cancer in recent years, there are still many patients who do not respond well to existing treatments. Therefore, finding new therapeutic strategies to improve patients' treatment response and quality of life is an important goal of colorectal cancer research.

In this context, we will explore in this review how the gut microbiome affects the response of patients with colorectal cancer when they receive chemotherapy. We will discuss the composition of the gut microbiome and how it influences the biological behavior and treatment response of tumors by influencing pathways such as immune response, metabolic status, and gene expression. In addition, we will explore whether the efficacy of chemotherapy can be enhanced by tweaking the gut microbiome, providing new strategies for improving the treatment of colorectal cancer.

2. Gut microbiome and colorectal cancer

The gut microbiome is a complex ecosystem located near the colorectal epithelium, composed of hundreds of billions of microorganisms, including bacteria, viruses, fungi and protozoa, whose composition is stable in infancy, but may undergo minor changes with age into adulthood and old age[7]. These microorganisms form a complex reciprocal relationship with the host, regulating many physiological processes such as energy harvesting, metabolism, and immune response. WillemMdeVos et al. clearly pointed out that "gut microbiota is now considered to be one of the key factors that help regulate host health"[8]. Such interactions are good for both microbial survival and host health. The two exist in a dynamic balance between symbiosis and pathogenesis, and when this balance is upset, the gut microbiome may transform from a beneficial "partner" to a potential pathogen that causes or promotes the development of multiple diseases, including tumors.

As a common malignant tumor of the digestive system, colorectal cancer (CRC) is the third most frequently diagnosed cancer in the world and the second leading cause of cancer death[9]. In recent years, the incidence and mortality of CRC in

China have been on the rise[10]. With the continuous progress of diagnosis and treatment technology, many new strategies have emerged for the treatment of CRC. However, chemotherapy, as the core treatment method of cancer, still plays an important role in the treatment of colorectal cancer, such as shrinking tumors to facilitate surgical resection and destroying cancer cells. However, adverse side effects of chemotherapy on patients such as gastrointestinal toxicity and hematological diseases and poor treatment response are also the main reasons for recurrence and poor prognosis of patients with colorectal cancer[11], so it is urgent to explore and improve treatment methods for colorectal cancer.

Multiple studies have revealed a link between the gut microbiome and colorectal cancer. By sequencing and comparing the gut microbiome of colorectal cancer patients and healthy people, multiple studies have shown that there are significant differences in the abundance of certain microbial species in colorectal cancer patients and healthy people[12-14]. Among them, metagenomic analysis of fecal samples from colorectal patients detected porphyromonas glycosolysaccharides and Streptococcus oris with abnormally elevated expression levels[15]. Similarly, KosticAleksandarD et al.'s study showed that *F. nucleatum* in CRC patients was significantly increased compared with healthy patients[16]. These microorganisms may influence the occurrence and development of colorectal cancer by influencing the immune response, metabolic status and gene expression of the host.

First, gut microbes may be directly involved in the development of colorectal cancer. Changes in intestinal microbiome may lead to colorectal cancer through the production of microbial metabolites or inflammatory diseases[17-19], among which enterococcus faecalis infection induces DNA damage of intestinal epithelial cells through the formation of superoxides, leading to CRC[20-21]. In addition, *Fusobacterium F. nucleatum*, which is significantly overexpressed in patients, can spread in the colon region, causing inflammation in the colon, and then lead to colorectal cancer[22-23]. Therefore, intestinal microorganisms may play an important role in the formation of CRC.

Second, gut microbes can also influence the development of colorectal cancer by altering the host's immune response. Some microorganisms such as *Fusobacterium* can stimulate the immune system, leading to activation of pro-inflammatory factors and recruitment of inflammatory cells[24], which may lead to malignant transformation of cells and the occurrence of colorectal cancer. In addition, some microorganisms can also help tumor cells evade immune surveillance by suppressing the response of the immune system, among which *Fusarium nuclear* can promote the development of colon tumors by down-regulating the adaptive immunity mediated by anti-tumor T cells[25].

Finally, gut microbes may influence tumor development by influencing host metabolic status and gene expression. *Fusobacterium* can produce virulence factor FadA to reduce the expression of E-cadherin while enhancing the β -catenin signaling pathway, affecting the metabolism and growth of colorectal cancer cells[26]. In addition, some microorganisms can also influence gene expression and signaling in host cells by producing small signaling substances, such as short-chain fatty acids.

Overall, the gut microbiome is closely involved in the occurrence and development of colorectal cancer through multiple mechanisms, which provides new perspectives for us to understand the biological behavior of tumors and develop new therapeutic strategies.

3. Gut microbiome and chemotherapy response

The gut microbiome is not only related to the occurrence and development of tumors, but also can affect the effectiveness of tumor treatment. The gut microbiome has been found to influence how patients respond to chemotherapy. The study of Noriholida et al. showed that the disruption of gut microbiota could impair the response of subcutaneous tumors to platinum-based chemotherapy, while the imbalance of gut microbiota caused by antibiotic use could further lead to the poor response of tumor-infiltrating bone marrow derived cells to chemotherapy[27]. A number of studies have found that the gut microbiome may affect the effect of chemotherapy through a variety of mechanisms[28-29].

First, gut microbes can alter the efficacy of drugs through their metabolic activity. Many studies have pointed out that gut microbes have an important impact on the efficacy and side effects of various drugs[30]. Among them, cyclophosphamide is one of the clinically important cancer treatment drugs. After administration, bacteria in the intestine will stimulate the production of a specific subset of T helper cells 17 (Th17), and the adoptive transfer part of pTh17 cells will restore the anti-tumor effect of cyclophosphamide[31], thus contributing to the anti-tumor effect of this drug. However, ilicitocan (CPT11), which is widely used to treat CRC, produces SN-38, which is toxic to intestinal epithelial cells under the metabolic action of intestinal microorganisms, and is thought to aggravate diarrhea in up to 80% of CRC patients[32-33], and may require discontinuation of the drug in severe cases. It can be seen that some bacteria in the gut microbiome can convert certain chemotherapy drugs into their active forms, thereby enhancing their anti-tumor effects. However, there are also some bacteria that can convert chemotherapy drugs into ineffective or more toxic forms, reducing their efficacy or increasing their

side effects.

Second, the gut microbiome may also influence the effectiveness of chemotherapy by modulating the host's immune response. A study by AnnaLouisePouncey et al. showed that "alterations in the immune response of the microbiome play a key role in determining the response to chemotherapy"[34]. For immune response, some microorganisms can stimulate the immune system through toll-like receptors and interact with innate and adaptive immune responses to regulate inflammatory response[35-36], which may enhance the killing effect of chemotherapy drugs on tumor cells. Gene expression analysis has shown that intestinal microorganisms promote oxaliplatin therapy by inducing the expression of pro-inflammatory factors[27]. On the other hand, some microorganisms may suppress the immune response, thereby reducing the effect of chemotherapy. NorihoIida et al. studied the influence of the interaction between microbiota and myeloid cells on the efficacy of chemotherapy in a mouse lymphoma model, and found that the production of inflammatory cytokines in myeloid cells and the body's adaptive immune response were reduced in sterile or antibiotic-treated mice with damaged intestinal microorganisms, which could be effectively improved by adding microorganisms through exogenous inoculation[27].

In addition, changes in the gut microbiome may also be associated with side effects associated with chemotherapy. Many factors in the course of anti-cancer treatment, such as surgical intervention, the use of adjuvant drugs (such as antibiotics) and the effect of chemotherapy, may change the community structure of intestinal flora[34], resulting in the disruption of the diversity and ecological balance of intestinal microbes, and the development of intestinal microbiome toward "disease accomplices". Chemotherapy can change the composition of intestinal microbiome. May result in reduced colonization resistance of pathogens and intestinal disorders such as diarrhea and wasting. These side effects not only affect the quality of life of patients, but also may lead to treatment interruption and affect the effectiveness of treatment.

Therefore, understanding how the gut microbiome affects chemotherapy response, and how to adjust the gut microbiome to improve chemotherapy outcomes, is an important direction of current research.

4. Adjust intestinal microbiome to improve chemotherapy efficacy

In view of the important influence of intestinal microbiome on chemotherapy response, in recent years, researchers began to use intestinal microbiome as a "drug target" to explore the adjustment of intestinal microbiome to improve the efficacy of chemotherapy. This may include the use of antibiotics, probiotics or microbiome transplants. These strategies aim to change the composition of the gut microbiome to make it more conducive to the effects of chemotherapy. Research in this area is still in its early stages, but there have been some promising results.

First, one possible strategy is to use probiotics, or prebiotics, to change the composition of the gut microbiome. Probiotics, including *Clostridium difficile*[37] and *Staphylococcus aureus*[38], can restore the ecological balance of intestinal microorganisms by competing for resources and space, and inhibit the growth of harmful microorganisms by antagonizing pathogen colonization[39]. Prebiotics are food components that cannot be digested by the human body and can improve the health of the host by selectively stimulating the growth and activity of bacteria that already exist in the colon[40]. The study of et al. pointed out that probiotic intervention can increase the abundance of bacteria that can produce butyrate in the flora, including *Bacillus faecalis* and *Clostridium*[29]. Meanwhile, according to the study of et al. , the bacteria associated with colorectal cancer will be reduced due to the use of probiotics, such as *Clostridium* and *Streptococcus gastricus*[41]. Therefore, the use of probiotics or prebiotics can change the composition of the gut microbiome, thereby improving the effectiveness of chemotherapy.

Another possible strategy is to use fecal microbial transplantation (FMT). FMT is a method of transplanting microbes from the stool of a healthy person into a patient that can rapidly change the composition of the recipient's gut microbiome to restore microbial homeostasis. Some earlier studies have found that FMT can improve treatment response in some patients with chemotherapy-resistant tumors. Laboratory mice reconstructed with natural microbiota in the et al study showed reduced inflammation and increased survival after influenza virus infection, as well as improved resistance to inflammation induced colorectal tumorigenesis[42]. As a new therapeutic method, FMT has significant advantages in other therapeutic strategies, but its application in tumor still needs further exploration.

In summary, the impact of changes in the composition and function of the gut microbiota may be part of the risk assessment process for new drugs[43], but the application of these strategies still faces many challenges. We don't yet know which microbes are beneficial and which are harmful. In addition, each person's gut microbiome is unique, so the same strategy may have different effects on different people. So we need more research to understand how to most effectively tune the gut microbiome to improve the effectiveness of chemotherapy.

5. Conclusion

Although we already know the important role of the gut microbiome in tumor development and treatment, many questions still need to be addressed. Here are some possible future directions for research: First, we need to gain a deeper understanding of how the gut microbiome affects the biological behavior of tumors. This includes understanding which microorganisms and their metabolites can influence tumor initiation, development, and metastasis, as well as the detailed mechanisms of these processes.

Second, we need to better understand how the gut microbiome affects the effectiveness of chemotherapy. This includes understanding which microbes can influence the metabolism and immune response of drugs, and how this knowledge can be used to improve the efficacy of chemotherapy.

Third, we need to develop more effective strategies to tune the gut microbiome to improve the effectiveness of chemotherapy. This could include developing new probiotic or prebiotic products, or optimizing ways to transplant fecal microbes.

Finally, we need more clinical trials to validate these strategies in the real world. This includes evaluating the safety, efficacy, and suitability of these strategies, as well as identifying which patients may benefit from these strategies.

Overall, the study of the gut microbiome in tumor development and treatment is a new area full of challenges and opportunities. Through in-depth research and the development of new treatment strategies, we are expected to improve treatment outcomes and quality of life for patients with colorectal cancer.

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