



FAECAL TRANSPLANTATION AS A POTENTIAL NEW APPROACH IN TREATING COLORECTAL CANCER

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Summary

Colorectal cancer is one of the leading causes of death in modern times and the most common form of cancer, whose number of patients is growing exponentially. Current treatment methods include surgery, chemotherapy, radiotherapy, and immunotherapy. However, although satisfactory, they have a large number of limiting factors. Inevitably, we consider the additive value of the new methods, such as fecal transplantation. Fecal transplantation is based on suppressing cancer metastasis by establishing a balanced and diverse intestinal microbiome in the affected person. In addition, it induces cancer cell apoptosis with its metabolites. It also stimulates the production of other molecules with the same function, making it a promising approach to treating colorectal cancer.

KEYWORDS: *intestinal microbiome, intestinal dysbiosis, fecal transplantation, colorectal cancer*

INTRODUCTION

With 1,93 million new cases per year and 916,000 deaths, colorectal cancer (CRC) is the second most common cause of death due to cancer. It affects 1 in 23 males and 1 in 25 females, which makes it the third most frequently occurring cancer globally(1,2). Numerous treatment strategies to fight CRC are currently in use. However, there are still no available medical treatments that completely eradicate this disease, which highlights the need for new therapeutic approaches. With the emergence of sequencing methods and the discovery of the gastrointestinal tract microbiome, numerous studies have confirmed the role of the intestinal microbiome in overall human health. It has been shown that a balanced and diverse intestinal microbiome, through its metabolites, affects the prevention and control of many diseases, including colorectal cancer. As a result, fecal transplantation has been explored as a promising treatment method, which will be further elaborated in this article.

CURRENT TREATMENT METHODS IN TREATING COLORECTAL CANCER

The standard therapies for colorectal cancer (CRC) include surgical removal, chemotherapy, radiotherapy, and immunotherapy. Depending on whether the tumor is resectable or non-resectable and the cancer stage, they can be used separately or in combination. Although surgical removal is considered the best approach for removing malignant solid tumors at an early stage and when the cancer is well-defined, chemotherapy and radiotherapy are the ones mainly used for advanced-stage tumors. Both methods are based on destroying cancer cells by damaging their genetic material that controls how cells grow and divide(3,4). On the other hand, immunotherapy uses medicines (immune checkpoint inhibitors) to improve the ability of a person's immune

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system to recognize and destroy cancer cells. Also, due to immunomodulating features, there should be an optimal time window to combine immune checkpoint inhibitors with other defined drugs to achieve maximum efficiency while controlling toxicities(4). Even though these therapies may prolong the patient's life, they can be non-specific and cytotoxic to normal cells and cause inevitable damage to normal tissues and organs, especially the immune system, often making the patient even more vulnerable to infections and new malignancies(4). Also, half of the patients have the problem of acquiring multidrug resistance. Cancer cells resist the effects of chemotherapeutic drugs in various ways, including drug inactivation, drug influx, efflux modifications, and ATP-binding cassette membrane transporter overexpression(5). Chemotherapy increases the relative abundance ratio of the Firmicutes/Bacteroidetes, inducing greater disturbance of intestinal microbiota(6), also called dysbiosis.

NEW METHODS IN TREATING COLORECTAL CANCER

To overcome the disadvantages of standard CRC treatment methods, new approaches have been developed, which can be divided into the following categories(7):

- a) RNA-based therapy
 - small interfering RNA (siRNA)
 - microRNA (miRNA)
 - RNA aptamer
- b) oncolytic viral therapies
- c) nanomaterials
- d) microbiome-based therapies
- e) cytokine-based medication

The regulatory functions of RNA are well known in nearly all physiological and pathological processes in the body, including carcinogenesis, which makes RNA-based therapy a promising approach. Besides that, many studies have shown that miRNAs are dysregulated and that ncRNAs are overexpressed in CRC patients, demonstrating they have good diagnostic value for CRC screening. Furthermore, miRNA/siRNA combinatorial therapy with various chemotherapeutic and immunotherapeutic agents increases the sensitivity of these drugs to cancers(7). New methods based on nanomaterials designed as carriers in drug de-

livery systems have also shown great promise in anticancer treatment(8). Oncolytic viral therapy or immuno-oncolytic virotherapy employs native or sometimes genetically modified viruses called oncolytic viruses to infect cancerous cells while avoiding healthy ones predominantly. It has emerged as a promising treatment option for CRC, with its ability to induce systemic antitumor immunity and selective replication within neoplastic cells that have a direct lytic effect on the tumor cells. Various cells, primarily immune cells, secrete cytokines that increase reactive natural killer (NK) cells and T lymphocytes, encourage lymphocyte infiltration of tumors, and persist in the tumor microenvironment. Unfortunately, more research is needed due to the complex network of cytokines in immune responses and unexpected toxicity(9).

FAECAL TRANSPLANTATION

One of the newly investigated approaches in treating colorectal cancer is improving the balance of the gut microbiome via fecal transplantation. It is based on transferring the intestinal microbiome from a healthy person to a sick person, most often by an enema.

An imbalance in the gut microbiota promotes the progress of colorectal carcinogenesis via multiple mechanisms, including inflammation, activation of carcinogens, and tumorigenic pathways, as well as damaging host DNA(10). After all, 70-80% of the human immune cells are located in the gut, so it's expected that the disturbance of the intestinal microbiome will affect a person's overall health, especially in the gastrointestinal system(11). Research on mice in which dysbiosis of the intestinal microbiome and colorectal cancer was induced showed that fecal transplantation from healthy mice reduced cancer progression and prolonged survival rates. Also, there was a massive infiltration of immune cells in the mice that received fecal transplantation, including CD8 + T and CD49b + NK. The number of immunosuppressive cells Foxp3 + Treg cells was also reduced compared to the number before fecal transplantation(12). Research has shown that a different gut microbiota profile was observed in patients with CRC compared to healthy people. The abundance of some bacterial taxa increased, such as Porphy-

romonas, Enterococcus, Streptococcus, and Peptostreptococcus. Conversely, some bacteria, such as Roseburia and other butyrate-producing bacteria in the family Lachnospiraceae, decreased quantity(12). Besides the change in the gut microbiome due to fecal transplantation, intestinal inflammation was also suppressed. Namely, the increased number of beneficial antiinflammatory bacteria such as Lactobacillus stimulates the recruitment of immune cells and down-regulates IL1a, IL6, IL12a, IL12b, IL17a, and elevates IL10(10). Additionally, the expressions of cytokines that were able to directly kill cancer cells, such as TNF α , IFN γ , and CXCR4, were positively correlated with Odoribacter, Lachnospiraceae UCG-006, and Desulfovibrio, found in gut microbiome after fecal transplantation. Furthermore, short-chain fatty acids produced by Lachnospiraceae help maintain intestinal barrier integrity and directly induce apoptosis of cancer cells. By acting on the FFAR2 receptor or directly on T-lymphocytes, they regulate their differentiation, recruitment, activation, and cytokine secretion(12,13).

CONCLUSION

Based on the latest discoveries and research, it can be concluded that standard approaches for treating colorectal cancer are not sufficient. The personalized approach mainly covers precision medicine via targeted drugs. However, vast areas of complementary systems and methods should be equally explored and integrated. Amongst them, a plan based on establishing diverse and balanced gut microbiomes has shown to have an essential role in regulating and suppressing carcinogenesis. Not only do specific bacterial species increase the number of immune cells, including NK cells, but they also stimulate cytokine production, which can directly eliminate cancer cells. Further research is needed to find the right use.

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Sažetak

FEKALNA TRANSPLATACIJA KAO NOVI POTENCIJALNI PRISTUP
U LIJEČENJU KOLOREKTALNOG KARCINOMA

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Kolorektalni karcinom jedan je od glavnih uzročnika smrti modernog doba i najčešći oblik karcinoma čiji broj oboljelih eksponencijalno raste. Aktualne metode liječenja se temelje na operativnom zahvatu, kemoterapiji, radioterapiji i imunoterapiji. Međutim, iako zadovoljavajuće, ove metode imaju veliki broj ograničavajućih faktora. Kako bi se oni nadvladali, počele su se razvijati nove metode od kojih se ističe fekalna transplantacija. Fekalna transplantacija se temelji na supresiji metastaziranja raka uspostavljanjem uravnoteženog i raznolikog crijevnog mikrobioma kod oboljele osobe. Pored toga, uravnoteženiji mikrobiom svojim metabolitima inducira apoptozu stanica raka i potiče proizvodnju drugih molekula s istom funkcijom. To ju čini obećavajućim pristupom u liječenju kolorektalnog karcinoma.

KLJUČNE RIJEČI: *crijevni mikrobiom, disbioza crijeva, fekalna transplatacija, kolorektalni karcinom*