Review

Probiotics in Cancer

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Abstract: In recent years, the consumption of over-the-counter probiotics used to promote health has grown rapidly worldwide and become an industry. In medicine, various studies have proven that probiotics can help improve the immune system and intestinal health. They are usually safe, but in some rare cases, they may cause concerning adverse reactions. Although the use of probiotics has been widely popularized in the public, the results of many probiotics clinical trials are contradictory. Especially for the cancer patients, the feasibility of probiotics management to provide benefits by targeting cancer and lessening anti-cancer side effects requires further investigations. And this review summarizes the interactions between probiotics and the host and current pros and cons of applying probiotics in the cancer patients.

Keywords: probiotics; cancer; safety; clinical trials

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1.Introduction

In the human intestine, there are more than 100 trillion symbiotic bacteria, far exceeding the number of host cells, which together constitute the intestinal flora.[1] They affect multiple functions of the host, and the stability of the intestinal flora is essential to prevent pathogen infection and disease.[2] The history of human consumption of probiotics can be traced back as early as 1907.[3] After a long and more than a century of screening, lactic acid bacteria and bifidobacteria have dominated the market. Among them, Bifidobacterium (adolescentis, animalis, bifidum, breve and longum) and Lactobacillus (acidophilus, casei, fermentum, gasseri, johnsonii, paracasei, plantarum, rhamnosus and salivarius) are the most used species on the market.[4] At the same time, there are some other strains seem promising to human healthy, such as Roseburia spp, Akkormansia spp and Faecalibacterium spp, which are worthy of in-depth study.[4]

In recent years, studies on the use of probiotics for prevention and treatment of human diseases have been carried out globally.[1] At present, a variety of beneficial mechanisms have been identified, including regulating intestinal flora, enhancing intestinal barrier function, protecting intestinal epithelium from invaded by pathogens and strengthening immune function.[5, 6]

Cancer patients have compromised immunity caused by primary diseases and chemotherapy and radiotherapy. The effects of probiotics on this population may differ from healthy people, which raises some critical concerns.[7] Therefore, this article makes a review on whether cancer patients could take probiotics and its pros and cons.

2.The effect of probiotics on the host

Studies have confirmed that probiotics can bring a variety of beneficial effects on the host. Besides, probiotic metabolites, such as short-chain fatty acids (SCFAs) and lactic acid also play a significant role.[4] A recent study found multiple probiotic metabolites could modulate host physiology by activating G protein-coupled receptors (GPCR) through a forward chemical genetic screening.[8] Based on the contribution of probiotics to intestinal health, it is currently believed that the core benefit of probiotics management is to maintain healthy intestinal flora and support healthy immune system through non-specific and specific physiological effects respectively.[1] (Figure 1)

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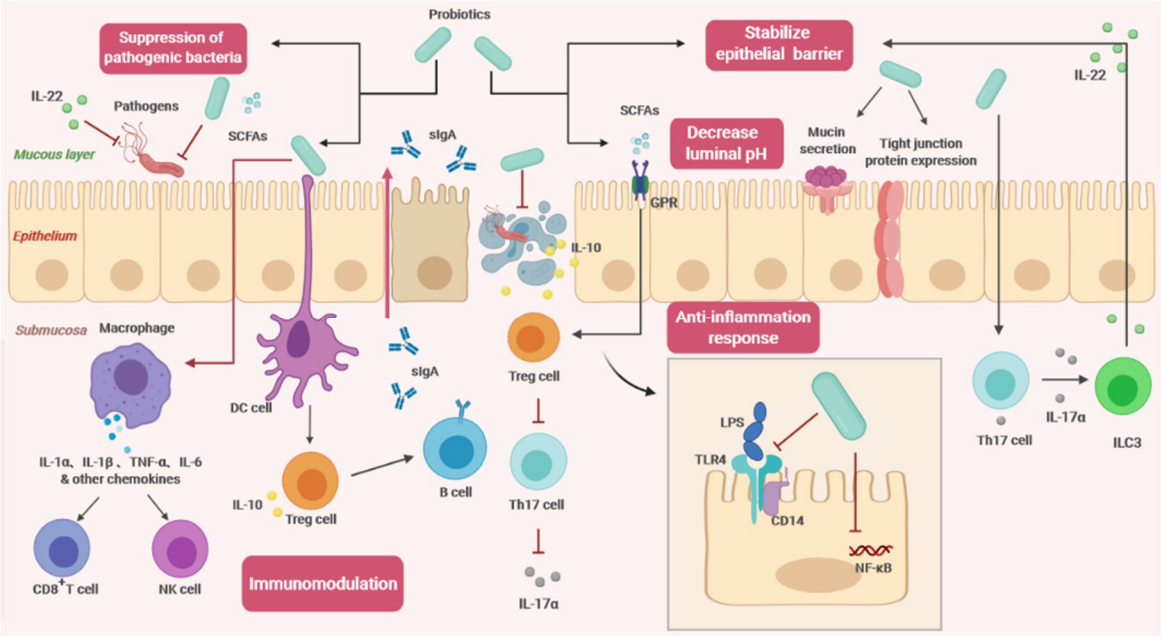

Figure 1. The effects of probiotics on the host

(SCFAs, short-chain fatty acids; sIgA, soluble IgA; GPR, G protein coupled free fatty acid receptor; DC cell, dendritic cell; Treg cell, regulatory T cell; Th17, T helper cell 17; ILC3, Type 3 innate lymphocyte; NK cell, Natural killer cell; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; NF-κβ, nuclear factor-κB)

2.1.Non-specific physiological effects

Regulate intestinal flora: probiotics can maintain a healthy balance of intestinal flora. By studying fecal specimens, it was found that supplementing with probiotics may increase the count of specific bacterial strains in healthy adults, thereby suggesting that probiotics may cause changes in the total number, diversity and composition of intestinal flora.[9] In the past, this has been used as an evaluation standard, but considering that fecal flora only reflect part of the intestinal flora information.[10] And the closer the sampling site is to the end of the rectum, the less it can reflect the structure of the upper flora. In a large-scale genomic analysis, it showed that fermented foods were indeed an important source of intestinal lactic acid bacteria, thus providing unprecedented evidence that food-derived probiotics were closely related to the composition of intestinal microorganisms.[10]

Stabilize intestinal epithelial cell barrier: probiotics could regulate the cytoskeleton to stabilize the mucosal barrier, and also promote mucin secretion to prevent the colonization of pathogens in the epithelium.[11] They could induce the expression and distribution of tight junction proteins.[12] And by sealing the top epithelium and endothelium, the increase in epithelial permeability and damage to the epithelial structure were prevented. Probiotics could also restore the abnormal transepithelial resistance caused by pathogenic lipopolysaccharide (LPS), thereby reducing the inflammatory response and excessive apoptosis.[12] In addition, certain probiotic strains regulated the polarization of T helper cell 17 (Th17) and effectively induced the secretion of IL-17α, which can trigger Type 3 innate lymphocyte (ILC3) to product IL-22.[6] IL-22 is a key immune defense cytokine, which plays an important role in maintaining intestinal homeostasis, promoting healing and tissue regeneration. Animal experiments revealed that mice lacking these cytokines are prone to occur experimental colitis due to defects in defensin secretion and damaged epithelial tight junction.[13]

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Inhibit pathogens: there are mainly two different mechanisms of inhibiting pathogens. One mechanism belongs to the physical defense. The infection of pathogens starts from colonization to the surface of the intestinal mucosa, thereby causing damage. When the probiotics completely occupy the space of the intestinal wall, there is no available space for pathogens, and probiotics that win the quantity can further inhibit the adhesion of pathogenic bacteria by obtaining more nutrients.[7] The other mechanism is related to the antagonistic properties of probiotics. Probiotics could reduce microenvironment pH by producing SCFAs.[11] Some studies found that SCFAs were mainly produced by the digestion of undigested carbohydrates by colon anaerobic bacteria, mainly including acetic acid, propionic acid, and butyric acid. The high concentration of SCFAs accumulated in the intestinal tract could quickly lower the pH value.[14] Compared with pathogens, probiotics are more able to adapt to lower pH environment and therefore have a better survival rate. In addition to changing the pH value, probiotics also antagonize pathogen adhesion and transport by other mechanisms.[7] A new study showed that IL-22 derived from intestinal flora regulated the mucosal glycosylation modification, promoted the growth of the symbiotic bacterium Koalabacterium, and could compete with Clostridioides difficile for succinate, thus preventing Clostridioides difficile infection.[15]

2.2.Specific physiological effects

Immune regulation：probiotics can regulate humoral immunity, innate immunity and cellular immunity through different mechanisms.[11] Despite some commonalities between probiotic and pathogenic surface molecules, intestinal epithelial cell could perceive and distinguish between symbiotic and pathogenic bacteria through cytokine production and signal transduction.[16] After probiotics came into contact with intestinal epithelial cell, the host dendritic cell (DC) accurately recognized probiotics surface and effector molecules through pattern recognition receptor and co-receptor, and then presented antigens to regulatory T cell (Treg) after processing.[17] The increase in the number of Treg promoted the transformation of B cell antibody classes and secretion of sIgA in large amounts.[18] Recent studies showed that in addition to the T cell-dependent pathways, sIgA production was also regulated through T cell-independent pathways.[19] This process was mediated by metabolite-sensing free fatty acid receptor.[19] After SCFAs bound to fatty acid receptor, it induced dendritic cell to express class 1A acetaldehyde dehydrogenase (Aldh1a), which converted vitamin A into retinoid acid, thereby assisted the production of sIgA.[19] In addition, probiotics could activate macrophage to secrete cytokine and subsequently activated the host natural killer cell and cytotoxic T cell, who could participate in immune response to clear pathogens.[16] SCFAs-mediated G protein-coupled free fatty acid receptor 43 (GPR43) signaling also caused NLRP3 inflammasome activation and secretion of IL-18 to further limit pathogens invasion.[20]

Anti-inflammatory response: there are both reports of probiotics inducing anti-inflammatory and pro-inflammatory responses. Although this may seem contradictory at first glance, it indicates that probiotics have an important balance effect on intestinal homeostasis in different context.[21] Through multiple signaling pathways, probiotics could regulate the expression of cytokines, chemokines, and antimicrobial peptides, including nuclear factor-κB (NF-κβ) pathway, mitogen-activated protein kinase (MAPK) pathway etc.[16] The role of probiotics in anti-inflammatory response was related to their ability to regulate Toll-like receptor (TLR) and GPR. Probiotics could stimulate negative regulatory factors (A20, Bcl-3, and MKP-1) to attenuate LPS induced TLR4 activation.[22] They could also inhibit the binding of LPS to CD14 receptor, thereby reducing the overall activation of NF-κβ.[23] After SCFAs bound to GPR, the regulatory function of Foxp3 $^{+}$ Treg cell became enhanced, increasing IL-10 production. It is well known that Treg cell has recognized protection in various inflammatory diseases, so SCFAs signaling can reduce the sensitivity to chronic

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inflammation.[24] Other study pointed out that GPR109A on the surface of dendritic cell and macrophage could recognize butyrate, promoted Treg cell development and inhibited the proliferation of pro-inflammatory Th17 cell.[20]

3.The effects of host on probiotics

In fact, it has been reported that the same strain has different effects on host physiology. Different from medicines, the efficacy of probiotics varies greatly from individual to individual. The age, physical condition, intestinal microbial composition, colonization permission and diet of the host, all contributed to the heterogeneity of the effect.[25] For infants and young children whose immune function is not yet fully developed, in the first month after birth, the development of intestinal flora is essential for the balanced development of the baby's immune system, although Bifidobacterium in breast milk is not only non-cytotoxic but also has good immunostimulatory ability, but there is insufficient evidence to show that supplementing with probiotics is beneficial to infant health.[14] In an observational study, although probiotics supplementation increased the infant's sIgA response, the incidence of mucosa-related diseases was higher in early childhood.[26] Compared with healthy adults, the beneficial effects of probiotics exposure in infancy were not only limited, but also related to the increased infections in later life.[26]

For cancer patients, after undergoing treatments such as chemotherapy, radiotherapy or surgical eradication, the underlying medical conditions like cachexia combined with treatment-related side effects, the microenvironment is in a more complicated situation, which can directly lead to intestinal mucosal barrier destruction and frustration of immunity system function. Above changes were not conducive to the colonization of beneficial probiotics in the colon.[27] In individuals with colorectal cancer, reduction in the number of probiotics was found.[28] Zmora, N. et al found that host ’s local intestinal microbes also played a central role in the colonization of probiotics, and useful function of probiotics was dependent on the support of the intestinal flora.[29] These results indicate that even if the probiotics used are beneficial, the colonization barrier will greatly affect the therapeutic effect. And there is an urgent need to elucidate the effects of probiotics on people such as cancer patients.

The intestinal microecology is composed of intestinal flora, prebiotics and enteral nutrition, which complement each other. Therefore, probiotics need a suitable environment to function. And it was needed to add a variety of foods to maintain a healthy flora.[30] For example, fermentable carbohydrates could support the colonization and growth of beneficial bacteria in the intestine.[31] And dietary fiber could stimulate the growth and activity of beneficial bacteria, and can reduce stomach acid to protect the probiotics to pass smoothly. Polyunsaturated fatty acids would regulate the adhesion of probiotics.[9] For cancer patients, in addition to individual factors, dietary difficulties, and the occurrence of malnutrition would accelerate the collapse of intestinal homeostasis caused by cancer. In this vicious circle, the therapeutic effect of probiotics was greatly reduced.[32]

4.Probiotics to prevent and treat cancer

In pre-clinical experiments, potential anti-tumor products include probiotics and their metabolites, such as butyrate and pyridoxine. These specific microbial strains can be used either alone or in combination with cancer treatment agents. The goal of treatment was achieved by activating immune surveillance against cancer.[20] For example, Shi L et al found that the combined treatment with TGF-β receptor blockers and probiotics could enhance the anti-tumor immune response, thereby inhibiting the growth of tumors.[33]

Studies have pointed out that the mechanisms involved in the anti-cancer of probiotics mainly include: positive regulation of intestinal flora and changes in metabolic activity, binding and degradation of carcinogenic compounds, immunomodulation to improve chronic

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inflammation, lowering intestinal pH and inhibition of enzymes that produce potential carcinogenic compounds.[28, 34] (Figure 2) The positive role of probiotics in the treatment of tumors has been confirmed at least in animal models.[35, 36]

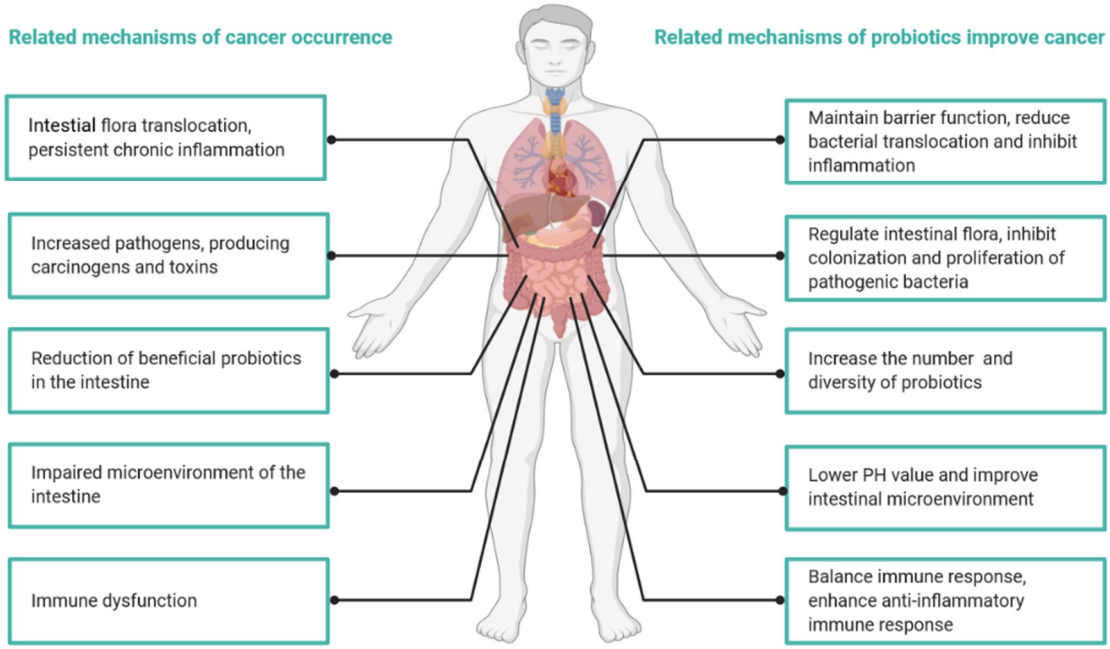

Figure 2. Mechanisms related to cancer occurrence and the mechanisms by which probiotics improve cancer

Abnormal composition of the intestinal flora was a high-risk factor for colorectal cancer.[37] The intestinal flora of patients with colorectal cancer usually contained a greater proportion of bacteria that cause gastrointestinal inflammatory diseases and bacteria that can produce toxins and carcinogenic metabolites.[38] On the contrary, SCFAs-producing bacteria and potentially beneficial probiotics showed a decreasing trend.[28] It is well known that chronic inflammation can make individuals susceptible to cancer.[39, 40] Studies found that under the mucus layer of the colon, Clostridium spp was in direct contact with colon cells, which invaded the submucosa of the colon and caused persistent local inflammation.[34] In addition, more Clostridium spp were found in colorectal cancer tissues, and they also showed a profile of inflammation-related genes and proteins, such as COX-2, NF-κB, TNF-α, IL-6, IL-8 and IL-12, and matrix metalloproteinases 3 and 9, all of which contributed to the tumor occurrence and transfer.[28] Chandel D et al found that use of Lactobacillus rhamnosus GG, Lactobacillus acidophilus, or in combination with celecoxib in colorectal cancer animal model, could reduce NF-κB, COX-2, β-catenin, K-ras carcinogenic biomarkers.[41]

Compared with non-cancer patients, the microbial structure of the sample tissue from colorectal cancer patients was significantly different, and the diversity was lower.[42] Treatment with probiotics increased the number and diversity of mucosal microorganisms and improved the microbial structure.[43] Pyrosequencing also showed that probiotics could significantly reduce the abundance of Fusobacter genus, which was previously suggested as a contributing factor to tumorigenesis.[44] Another pre-clinical study claimed that Bifidobacterium bifidum and L. acidophilus could be used as biotherapeutic agents to inhibit colon cancer by modifying intestinal bacteria.[35] And for people who are highly susceptible

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to colorectal cancer, probiotics might be used as an alternative biological therapy to prevent or even treat cancer.[35]

In addition to gastrointestinal tumors, abnormal changes in the composition and function of intestinal microbes could also affect non-gastrointestinal tumors, including liver cancer, pancreatic cancer and even breast cancer.[27, 45] Through the portal venous system, the liver is uniquely exposed to intestinal bacteria and their metabolites, which may cause inflammatory changes and hepatotoxicity, and ultimately directly lead to cancer. It has also been widely recognized that disturbance of intestinal flora may cause liver cancer.[46] For example, Haemophilus is a common pathogenic bacteria colonized on the colonic mucosa. And it was detected in human liver cancer tissues.[20] Studies believed that Haemophilus can produce a lethal dilatant toxin after translocating to the liver and activate liver cell Wnt / β-catenin, NF-κB, p21 and Ki67 signaling to induced liver cancer.[20]

By constructing a mouse liver cancer model, Li j et al confirmed that treatment with probiotic E. coli Nissle 1917 enhanced the anti-tumor immune response, thereby inhibiting tumor progression.[36] The specific mechanism was that Th17 cells and their product IL-17 were reduced in tumor tissues, and the differentiation of Treg / Tr1 cells were enhanced, which affected the expression of vascular growth factors, and suppressed the progress of liver tumors in terms of inflammation and angiogenesis.[36]

Recent study by Le Noci, V et al showed that probiotics aerosol therapy was beneficial to inhibit lung melanoma metastasis.[47] The lung microenvironment had high immune tolerance, and this feature could prevent excessive inflammation caused by inhaled air particles.[48] However, it also provided conditions for lung metastasis of various tumors.[48] Lactobacillus rhamnosus could induce the maturation of resident antigen-presenting cells, further activated lung T cells and NK cells, and improved the immune suppression state, and thus enhanced the anti-tumor immune effect.[47] And when used in combination with the chemotherapeutic drug dacarbazine, the efficacy was significantly enhanced. And probiotics aerosol therapy has become a new clinical therapy to prevent lung metastasis in high-risk melanoma patients.[47]

Although the intestinal flora is not a necessary condition for the anti-tumor effect of chemotherapeutic drugs, experiments found that the survival rate of sterile or flora depleted mice was significantly reduced.[49] After treatment with lactic acid bacteria, the anti-cancer effect of chemotherapeutic drugs was restored. These results indicated that the flora might assist the chemotherapy effect through a flora-dependent mechanism.[49]

5.The role of probiotics in the treatment of anti-tumor side effects

Gastrointestinal reaction is a common side effect of anti-tumor therapy. Radiochemotherapy directly kills intestinal cells and the stress response it causes would lead to destruction of intestinal mucosal barrier. In the case of increased permeability of the intestinal mucosa, intestinal flora and endotoxins enter extraintestinal tissues and organs, causing uncontrolled systemic inflammation and multiple organ failure.[50, 51] Surgery may result in impaired physiological gastrointestinal function. Diarrhea can be caused by a significant reduction in the transit time of food through the intestines and excessive bacterial growth.[52] Antibiotics are often used during treatment, which can also affect the microbiome.[53] Probiotics based on Bifidobacterium and Lactobacillus can effectively resist the growth of harmful bacteria through biological action.[54] Supplementing probiotics can improve the intestinal environment, enhance intestinal mucosal barrier function, and reduce the occurrence of diarrhea.[52, 54] Recent studies found that the improvement of anti-tumor side effects by probiotics was also related to innate immunity. For example, probiotic cell wall acyl dipeptides could alleviate mucosal damage caused by antibiotic chemotherapeutics by stimulating intracellular pattern recognition receptors (NOD2).[49] In general, probiotics may have a beneficial effect on improving diarrhea caused by radiochemotherapy or surgery,

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and rarely cause side effects.

In addition to restoring the intestinal mucosal barrier, probiotics can also improve oral mucosal damage induced by chemotherapy. In the past clinical treatment, more than 70% of hematological patients receiving high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT) may develop grade III or IV oral mucositis, which brings great pain. Atul Sharma et al analyzed the efficacy of Lactobacillus CD2 in preventing grade III / IV mucositis in patients receiving HSCT.[55] Only 19% of patients developed grade III or IV mucositis. The median time to onset and recovery were 6 days and 8 days, and throughout the observation process, no adverse reactions related to probiotics were found.[55]

Probiotics also help in systemic inflammation, such as graft-versus-host disease (GVHD). Donor-derived T cells, pro-inflammatory cytokines, and LPS are the main triggers of GVHD, in which the intestine is one of the organs most affected by GVHD and a key determinant of GVHD severity. The occurrence of GVHD would greatly limit the feasibility and efficacy of HSCT.[56] A complete intestinal barrier plays an important role in the development of GVHD, and LPS can enter the circulatory system through the damaged mucosal barrier to induce GVHD.[57] In animal experiments, oral administration of L. rhamnosus GG before and after transplantation improved the survival rate of mice, especially between the 7th and 14th days after transplantation, and the reduction in mortality was even more pronounced.[58] Probiotic administration in patients receiving HSCT may also reduce the incidence of stage III-IV acute GVHD. One ongoing study showed that probiotics supplementation therapy reduced the bacterial translocation of mesenteric lymphoid tissue and the reduction of terminal ileal histological inflammation, indicating that probiotics can indeed improve GVHD.[59]

Emerging data indicated that there was a strong correlation between abnormal microbiota composition and intestinal manifestations of acute GVHD.[60] Although it has been observed that probiotics can improve GVHD in animal models, the mechanism is poorly understood. There were reports that SCFAs could directly act on intestinal epithelial cells to promote recovery.[60] Studies also shown that IL-22 played an important role in mediating the recovery of intestinal stem cells in GVHD, which might be related to its function of promoting Paneth cells to secrete antimicrobial peptides and mediating epithelial regeneration.[61]

Similarly, probiotics metabolites may also improve GVHD. Indole or indole derivatives metabolized by tryptophan in the intestinal flora can limit intestinal inflammation caused by various stressors.[62] Indole-3-carbaldehyde (ICA) (indole derivatives) reduced the intestinal bacterial translocation and inflammatory cytokine production in mice through type I IFN signaling.[62] In mice lacking type I IFN signaling, the protective effect of ICA was eliminated after radiation exposure.[62] These data indicated that indole could assist limit acute GVHD-related damage while retaining the anti-tumor response.[62] In general, intestinal GVHD is characterized by the destruction of integrity of the intestinal epithelial barrier and the disorder of flora. Therefore, probiotics and its production that remodel the microbial community, inhibit pathogens, reduce inflammation and restore intestinal epithelial barrier, might be a good treatment strategy for GVHD in the future.[63]

Compared with the lack of clinical data for probiotics to treat tumors, there were more clinical trials results proving that probiotics did have certain benefits in improving anti-tumor related side effects. (Table 1)

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Malignancy	Case number	Treatment strategy	Objective	Intervention	Outcome	Side-effect
Cervical cancer	54	Radiotherapy	Improve diarrhea	From day 1 to the end of radiotherapy, receive 3 capsules per day, each containing 1.75 billion live bacteria (Lactobacillus acidophilus LA-5 and Bifidobacterium animalis subsp BB-12)	The incidence of diarrhea in the probiotic group was lower than placebo group (53.8 and 82.1%, p <0.05), and the use rate of the anti-diarrhea drug loperamide was significantly reduced (p <0.01)	No probiotics -related toxicity reported
Colorectal cancer	150	Postoperative chemotherapy	Improve diarrhea	1-2×10^{10}Lactobacillus rhamnosus GG supplements daily	Patients receiving probiotics had mild diarrhea, and the incidence of grade 3 or 4 diarrhea (experimental group vs control group: 22% vs 37%, P = 0.027)	No probiotics -related toxicity reported
Lung cancer	41	Chemotherapy	Improve diarrhea	Starting one day before chemotherapy, take C. butyrate 3 times a day (420 mg/tablet) for 3 weeks	The incidence of grade I diarrhea was lower in the probiotic group (20% and 42.86%)	No probiotics -related toxicity reported
Gastric cancer	120	Surgery	Improve diarrhea	Nutrient formula food rich in fiber and probiotics, providing enteral nutrition for 7 consecutive days after surgery	Diarrhea cases decreased in combination of fiber and probiotics group	No probiotics -related toxicity reported
Head and neck cancer	200	Radiotherapy and chemotherapy	Improve oral mucositis	From the first day of treatment to 1 week after the last treatment, Lactobacillus brevis CD2 tablets (not less than 2×10^{9}), 6 times a day	The incidence of grade III and IV mucositis in the probiotics was lower than placebo group (52% and 77%, P <0.001), the completion rate of anticancer treatment in probiotic group was significantly improved (92% and 70%, P = 0.001)	No probiotics -related toxicity reported
Colorectal cancer	52	Surgery	Improve inflammation	Starting 4 weeks after surgery, oral administration of 30 billion probiotic mixed preparations twice a day for 6 months	Inflammatory cytokines in probiotics group were significantly reduced, including TNF-α, IL-6, IL-10, IL-12, IL-17A, IL-17C and IL-22 (P<0.05)	No probiotics -related toxicity reported

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Table 1. Clinical trials using probiotics to improve the side effects of anti-cancer therapy

6.Safety assessment of probiotics

As additional supplementary active microorganisms, it must be considered the adverse reactions of probiotics, mainly including systemic infections, gastrointestinal side effects, skin reaction, access to antibiotic resistance genes, harmful effects of probiotic metabolites and abnormal stimulation of the immune system.[7] The population at highest risk includes infants, the elderly, hospitalized patients, and patients with immunodeficiency due to genetic or acquired diseases.[67] Studies showed that the incidence of bacteremia in patients using yeast is about 1 / 5.6 million, and lactic acid bacteria was lower than 1/1 million.[68] The result of another large-scale epidemiological study indicated that infections caused by Lactobacillus and Bifidobacteria were extremely rare, accounting for 0.05%-0.4% of the total cases of infective endocarditis and bacteremia, and most patients had severe underlying diseases.[69] In addition to being related to individual factors, the risk of infection was also related to the type and dose of the probiotics. It was reported that compared with Bifidobacterium, Lactobacillus was more likely to cause infection.[70, 71]

One of the most important theoretical issues in clinical use of probiotics is bacteremia, while fungal infections caused by yeast are even more difficult to treat. Compromised intestinal integrity and probiotics translocation are the main causes.[72] Genomics data confirmed that these adverse reactions were indeed related to ingested probiotics rather than colonized probiotics in the intestine.[73] It was found that for patients with impaired immune function, the risk of infection was greatly higher. Redman et al conducted a systematic retrospective study and found that five of 1530 patients reported probiotics-related bacteremia, although probiotics management indeed improved the severity and frequency of diarrhea in these cancer patients.[74] So in cancer patients, the serious invasive disease caused by probiotics deserves vigilance.[75-79]

In another systematic retrospective study, the currently managed probiotics strains (mainly Bifidobacterium, Lactobacillus), dosage (daily supplemental doses did not exceed $5.0X10^{10}$CFU / day, median was 2.0×10^9 CFU / Day), there were no serious adverse reactions caused by probiotics, the results showed that it was safe to use probiotics in patients with impaired immune function, including very severe patients. However, most of them focused on the efficacy of probiotics rather than safety, and large-scale clinical studies are needed to further prove their true safety.[80]

HSCT has become the standard treatment for many adult and childhood malignant tumor diseases, but the side effects caused by the treatment cannot be underestimated.[81] More and more evidence shows that the diversity of the microbiome will be disturbed during treatment, often leading to abnormal systemic immunity response and pathogen colonization and mucosal invasion. There were also studies showing that the loss of microbial diversity was an independent risk factor for the death of allogeneic HSCT.[82]

Probiotics protect the microbiome and can minimize the risk of gut-mediated diseases. However, their safety has not been fully evaluated in the case of HSCT. Recently, Ladas et al evaluated the safety and feasibility of probiotics in 30 children and adolescents who had undergone allogeneic HSCT.[83] In the time range that coincided with intestinal mucosal damage and accompanying neutropenia, no cases of probiotics bacteremia (0% (0/30), 95% CI 0-12%) were observed, and there were no other unexpected adverse events. Although new infection of C. difficile were found in 20% of the participants, studies confirmed that they were not related to probiotics management.[83] Their research provides preliminary evidence that the management of probiotics is safe and feasible in children and adolescents undergoing HSCT.[83] Another study showed that for patients who received unrelated cord blood transplantation, early stage yogurt supplementation was safe and feasible, no unexpected adverse events caused by probiotics were observed.[84] Therefore, for patients receiving

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HSCT, probiotics may have a positive role in maintaining the health of the intestinal flora and improving the prognosis of patients.

However, in one clinical study, it was believed that probiotics did not benefit patients with acute myeloid leukemia undergoing intensive treatment or bone marrow transplantation.[85] Instead, the probiotics treatment group had a higher incidence of infection, especially blood infection.[85] And the researchers concluded for patients with a long-term risk of neutropenia, without other indications of using probiotics, it was not recommended for such patients use probiotics.[85]

7.Conclusions

As a dietary supplement, probiotics lack strict standards for efficacy and safety certification. Although the effectiveness of several strains has been experimentally supported, the health-promoting effects of most probiotics are not proven. Relevant publicity of probiotic products rarely mentions the potential risks.

In a number of trials evaluating the protective effect of probiotics therapy on anti-tumor treatment-related side effects, the combined use of probiotics strains does have a positive protective effect for patients with certain immune functions.[46] However, for patients with severely impaired immune function, especially patients with neutropenia, careful consideration is required.[86] Due to the complex pathogenesis of tumors, and diverse interactions among patients, anti-tumor treatments and probiotics, large-scale clinical trials are urgently required.

Finding the most beneficial strains for the prevention and treatment of different types of cancer requires a very extensive human database as a basis, and it is necessary to carefully analyze the correlation between different strains and clinical responses. Once we have found a beneficial flora for cancer prevention and treatment, the next challenge is how to use probiotics and their products to regulate patient's flora. Besides, we can use the intestinal flora as a new cancer biomarker based on their response to the changes of the pathophysiological environment. The ultimate goal is to find specific strains or combination strains that can both reduce the side effects of cancer treatment and also help anti-cancer treatment.[87] Therefore, for cancer and other diseases, the regulation of targeted human flora is likely to become a new field of precision and personalized medicine in the future.

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