

Research on the correlation between intestinal microecology and leukemia

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Abstract. Intestinal microecology is the largest and most complex microecological community in the human body and is closely related to human health. About 20% of malignancies are associated with microecological dysbiosis. The gut microbiota of patients with leukemia is significantly different from that of the healthy population. The intestinal flora can be involved in the development and progression of leukemia in many ways through regulation of immune cells, stimulation of inflammation, infection by pathogenic bacteria, action of metabolites, influence of body metabolism and genetic mutations. Chemotherapy, allogeneic hematopoietic stem cell transplantation and chimeric antigen receptor T-cell immunotherapy can cause intestinal flora disorders in leukemia patients, and probiotic therapy can reduce the complications associated with the treatment process. The intestinal microecological stability is beneficial to the treatment of leukemia patients, therefore, the in-depth exploration of methods to maintain the intestinal microecological balance is important for the prolongation of survival of leukemia patients.

Keywords: leukemia; intestinal microecology; immunity; probiotics

1. Introduction

Leukemia is a group of malignant diseases of the hematopoietic system. According to GLOBOCAN 2020, leukemia accounts for 2.5% of all new cases of cancer and 3.1% of all cancer deaths worldwide [1]. In the latest epidemiological survey in China, the incidence of leukemia was 8.6% and the mortality rate was 5.6% [2]. The pathological mechanisms of leukemia have not been fully elucidated, but genetic abnormalities, epigenetic abnormalities, microenvironmental factors, and intestinal microecology play a key role in leukemogenesis. With the development of 16SrRNA gene sequencing technology, the study of microecology has become a hot research in malignancy [3]. The human gut has about 10^{14} bacteria belonging to hundreds of different flora, which together form a complex ecological chain in which microorganisms are interconnected with various aspects of the host [4]. Under normal organism, the intestinal microecology is in a relatively stable state and is closely related to the immune system of the organism, and the two together maintain the stability of the internal environment of the organism. When this balance is disturbed, the number of beneficial bacteria decreases and the number of opportunistic pathogenic bacteria increases, leading to a disruption of the integrity of the intestinal barrier, which in turn triggers a chain reaction of many diseases. Intestinal microecology is involved in the inflammatory response, immune response and metabolism of the organism, and microecological imbalances can lead to the development and progression of inflammatory diseases and tumors [5, 6]. In this paper, we mainly describe the current research progress related to leukemia in the field of microecology, and provide new ideas and directions for the diagnosis and treatment of leukemia in the clinical setting.

2. Intestinal microecological system

2.1. Basic concepts of intestinal microecology

A diverse microbiota exists in the organism's gut, on the skin surface and on almost all exposed surfaces [7]. Homeostasis between the microbiota and the host is maintained through the diversity of microorganisms, their colonization distribution, and complex molecular crosstalk between multiple

components of the whole organism [8]. Microecology is a diverse community of bacteria, fungi, protozoa and viruses present in the gut of all mammals [9]. It has been found that changes in intestinal microbial diversity and/or abundance are associated with a variety of tumors, such as the enrichment and absence of multiple flora in the gut of patients with colorectal cancer [10], and dysbiosis of the intestinal flora in patients with pancreatic, intrahepatic cholangiocarcinoma, hepatocellular carcinoma, and breast cancer [11-14]. Current studies have revealed that microorganisms can be involved in the metabolism of host substances and the development of several malignancies by modulating inflammatory and immune responses.

2.2. Main functions of intestinal microecology

Intestinal microecology plays a key role in the regulation of host digestion and metabolism. Through anaerobic fermentation, intestinal microorganisms are able to degrade undigested polysaccharides into a variety of short-chain fatty acids (SCFAs), mainly containing butyrate, acetate and propionate. And these substances are readily absorbed and utilized by colon cells as well as other tissue cells as a source of energy and carbon [15]. The differentiation and development of the body's immune cells are also influenced by the gut microbes. This process involves multiple transcription factors of the aromatic hydrocarbon receptor (AhR), Foxp3 and ROR γ [16-18]. Reg4-related microorganisms (*Lactobacillus*) in the gut can promote IL-35+ B cell production by producing indole-3-acetic acid (IAA) in the presence of lipopolysaccharide (LPS) stimulation [19]. The intestinal flora metabolites SCFAs promote both the development of regulatory T cells (Treg) and IL-10 production by CD4+ T cells [20-22] and IL-22 production by CD4+ T cells and ILCs through inhibition of GPR41 and HDAC [23].

3. Basic information of leukemia

Leukemia is a malignant neoplastic disease caused by abnormalities of the hematopoietic system. Its pathogenesis is the abnormal proliferation of primitive cells, which leads to disorders of their differentiation, rapid increase in number, uncontrolled proliferation and impaired apoptosis [24]. Patients have accumulation of leukemic cells in the bone marrow, blood and lymph nodes in the early stages. As the disease progresses tumor cells gradually infiltrate into other tissues, which in turn leads to spleen enlargement, abnormal liver function, enlarged lymph nodes, and fever from infection. The intestinal flora and the metabolites it produces play an important role in different aspects of the body's immunity, inflammation and infection, and are directly or indirectly involved in the process of leukemia formation.

4. Intestinal microecological imbalance and leukemia

4.1. Intestinal microecology and immunity

In the immune system within the organism, the site-specific phenotype and function of T and B cells in the mucosa are influenced by microorganisms that play a key role in maintaining immune homeostasis by suppressing harmless antigenic responses and enhancing the integrity of mucosal barrier function [25]. In addition, the flora can modulate intestinal adaptive immunity against pathogenic infections by promoting secretory immunoglobulin A (SIgA) production and regulating the balance of effector and regulatory T cells [26]. SIgA is the first line of defense to protect the intestinal epithelium from enterotoxins and pathogenic microorganisms by trapping antigens and pathogenic microorganisms in the mucus and removing them from the intestinal lumen through peristaltic and mucosal ciliary activity [27]. Reduced intestinal SIgA secretion in patients with leukemia leads to disruption of intestinal mucosal barrier integrity, invasion of intestinal toxins and pathogenic microorganisms, and stimulation of dendritic cells to produce different cytokines, leading to differentiation of T cells into different subpopulations [28]. In childhood B-cell acute lymphoid leukemia, the number of T cells differentiated into Tregs increases, thereby suppressing the ability to

coordinate host immunity [29]. When host immunity decreases, it may cause an imbalance in intestinal microecology, which leads to dysbiosis of normal flora and proliferation of conditionally pathogenic bacteria. For example, *Bacteroides fragilis* whose polysaccharide production (PSA) is recognized by dendritic cells and submitted to naive CD4⁺ T cells, leading to the production of TGF- β , which activates the secretion of IL-10 by Treg and suppresses the immune response [30], while Liu et al. further found that IL-10 gene diversity is closely associated with susceptibility and pathogenesis of childhood acute lymphoblastic leukemia [31]. In addition, this study found a negative correlation between *Lactobacillus* and tumor necrosis factor (TNF) expression, yet TNF can kill tumors by increasing tumor immunosensitivity [32]. Therefore, the stability of intestinal microecology is of great importance in maintaining the immunity of the organism.

4.2. Intestinal microecology and inflammation

The presence of inflammation can promote the development and progression of cancer and is involved in various pathological processes of tumorigenesis, growth and metastasis, thus there is a close correlation between inflammation and cancer [33]. Ramos et al. found that the presence of inflammation causes disruption of the intestinal barrier integrity [34]. The disruption of intestinal barrier integrity in turn allows the transfer of intestinal flora and their metabolites to the ruptured intestinal barrier, further triggering inflammation [35]. The stimulatory effect of various factors on the gut barrier gap causes excessive activation of NF- κ B (p65) in intestinal epithelial cells. In turn, the expression of p65 induces the production of miR-155, which ultimately leads to unlimited proliferation and differentiation disorders of hematopoietic stem cells and induces leukemia [36]. IL-1 α is also an inflammatory factor, which can be produced following the breakdown of the intestinal barrier and the onset of the inflammatory response, and can also be spontaneously expressed in primary cells of acute lymphoblastic leukemia (ALL). IL-1 α expression promotes the growth of leukemic cells through the activation of NF- κ B and SP1 [37]. In addition, Lee et al. revealed that microbiome-derived molecules, including bacterial DNA, which can reach the bone marrow through the bloodstream and lead to the production of inflammatory cytokines (TNF- α , IL-1, IL-6) after recognition by CX3CR1⁺ monocyte Toll-like receptor (TLR)-dependent mechanisms [38], all of which can be involved in the leukemic process.

4.3. Intestinal microecology and infection

Invasion of normal intestinal microecology by other pathogenic bacteria or disruption of its own homeostasis can lead to the development of gastrointestinal infections, and the incidence of leukemia is substantially increased in those with gastrointestinal infections, which may be related to immune dysregulation of the gut due to gastrointestinal infections. By studying animal models, it was found that pioneer B-cell acute lymphoblastic leukemia (pB-ALL) susceptible mice exposed to infected (mouse norovirus, mouse hepatitis virus, *Helicobacter* spp. and *Trichomonas*) environments showed a higher incidence of leukemia compared to homozygous mice raised in pathogen-free environments [39]. And Østgård et al. combined a large Danish medical database to conduct a national case-control study confirming that gastrointestinal infections are associated with an increased risk of developing acute myeloid leukemia (AML) [40]. In addition, the "delayed infection" hypothesis suggests that microbial exposure early in life facilitates a well-established immune system, whereas in the absence of microbial exposure, disruption of the immune system in susceptible children exposed to certain infections can trigger the development of leukemia [41]. Therefore, the stability of intestinal microecology plays a key role in the integrity of the intestinal barrier and contributes to the reduction of leukemia.

4.4. Intestinal microecological metabolites and leukemia

The metabolites of intestinal microecology have both advantages and disadvantages, and they may promote the progression of leukemia or be involved in the treatment of leukemia. McDonald et al. proposed the hypothesis that phenols produced by intestinal microorganisms are causative factors of

leukemia [42]. In animal models, the proportion of flora with the function of converting dietary flavonoids increases in the small intestine of leukemic mice [43], and Strick et al. found that bioflavonoid intake may be a factor in the pathogenesis of leukemia in infants and children [44]. However, anaerobic fermentation by intestinal microorganisms can degrade undigested polysaccharides into SCFAs, which in turn can be involved in the leukemia treatment process. For example, butyric acid produced by *Clostridium difficile* can promote differentiation of Treg cells and increase their ability to secrete IL-10 by inhibiting histone deacetylases [21]. Butyric acid can also induce macrophage metabolism and transcription by inhibiting histone deacetylase 3, thereby enhancing its antimicrobial activity [45]. Nakkarach et al. found that SCFAs produced by *E. coli* KUB-36 induced the expression of the anti-inflammatory cytokine IL-10 and inhibited the expression of the inflammatory factors IL-1 β , IL-6, IL-8 and TNF- α , acting as anti-inflammatory and anti-cancer agents [46]. Therefore, intestinal microecological metabolites have an important role in the pathogenesis and treatment of leukemia.

4.5. Intestinal microecology and metabolic processes of the body

Patients with leukemia are often combined with some metabolic diseases such as diabetes and hypertension. Basen-Engquist et al. found a higher risk of certain types of solid tumors and leukemia in the obese population, suggesting a link between tumor growth and metabolism [47]. One of the main metabolic features of cancer cell growth and proliferation is the disruption of glucose metabolism. Leukemic cells take up large amounts of glucose for their own rapid proliferation, and metabolites from the intestinal flora can be involved, but the exact mechanism is not yet clear. Abnormally active glycolysis in AML cells leads to a significant decrease in the glucose content of the bone marrow of patients [48]. And Ye et al. found that the production of short-chain fatty acids in the intestine of leukemic mice was significantly reduced in *Trichophyton* spp. and *Bacillus* spp. This can lead to an imbalance in intestinal microecology and trigger a decrease in insulin secretion, causing a disruption of glucose metabolism, and malignant cells can use the body's glucose to promote tumor growth [49]. Therefore, the abnormally active glucose metabolism and intestinal microecological imbalance in leukemic cells may play an important role in the development and progression of leukemia.

4.6. Intestinal microecology and gene mutations

There is a link between intestinal microecology and genetic mutations in leukemia patients. The TET2 gene, an oncogene, is located on chromosome 4q24 and plays an important role in epigenetics. Deleterious expression of mutations in the TET2 gene leads to genetic impairment of PD-L1 and Th1-type chemokines, while co-expression of PD-L1 and chemokines can serve to protect host tissues and suppress inflammation [50]. Mutations in the TET2 gene are commonly seen in a wide range of hematopoietic cancers including bone marrow and lymphoma, as well as several solid tumors [51]. The integrity of the intestinal wall can be disrupted by TET2 mutations, allowing bacteria present in the small intestine to enter the bloodstream and surrounding organs through the breach. As a result of the abnormal bacterial invasion, the body's immune system then responds with a corresponding immune response, expressing the appropriate inflammatory mediator (IL-6), which subsequently promotes the proliferation of hematopoietic stem cells and the formation of pre-leukemic myelodysplasia (PMP), whereas germ-free TET2 knockout mice do not show signs of myelodysplasia and antibiotics and IL-6 inhibitors can reverse PMP [52]. Therefore, mutations in TET2 in hematopoietic cells leading to disruption of the intestinal barrier and production of the inflammatory mediator IL-6 are essential for the development of PMP.

5. Intestinal microecology and the treatment of leukemia

Chemotherapy and hematopoietic stem cell transplantation, as well as the still cutting-edge immunotherapy with chimeric antigen receptor T-cell immunotherapy (CAR-T) cells, are the main

treatment options for leukemia. All three treatment modalities for leukemia can have an impact on changes in intestinal microecology, and certain specific flora can enhance the efficacy or mitigate the side effects of treatment.

Chemotherapy is one of the most commonly used methods for the treatment of leukemia. The effects of intestinal microorganisms and leukemia chemotherapy are reciprocal; chemotherapy affects the symbiotic relationship between microorganisms and the body, and disturbances in intestinal microecology affect the effects of chemotherapy. Among the drugs commonly used in chemotherapy are methotrexate (MTX) and cyclophosphamide (CXT), each of which has different effects on intestinal microecology. For example, MTX has anticancer and immunosuppressive properties, but Zhou et al. found that MTX administration leads to changes in the diversity and major components of the intestinal flora, especially a decrease in *Bacillus mimicus*, and verified the conclusion that the use of this drug leads to an imbalance in the intestinal flora and exacerbates the damage to the intestine [53]. CTX is also commonly used in chemotherapy, but the use of this drug exacerbates intestinal microecological dysbiosis, while Liu et al. found that fasted mice made a significant increase in lactobacilli in the intestinal microecology through a study of mice given CTX, which alleviated inflammation and improved intestinal barrier function, further aiming to reduce the side effects of cyclophosphamide [54]. Furthermore, in another study evaluating the effect of probiotics on chemotherapy-induced gastrointestinal side effects in patients with acute leukemia (AL), daily supplementation with probiotics (*Lactobacillus rhamnosus*) was found to reduce gastrointestinal side effects [55]. Therefore, the rational use of probiotics in chemotherapy can increase the efficacy and reduce the occurrence of side effects.

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is currently the most effective anti-leukemia treatment [56]. Graft-versus-host disease (GVHD) is a common complication of hematopoietic stem cell transplantation and affects the quality of life of patients [57]. It was found that GVHD patients target and modulate Pan cells, blocking the expression of the antimicrobial peptide α -defensin, which leads to loss of intestinal flora diversity [58]. Jenq et al. evaluated and analyzed the composition of fecal bacteria in 64 patients after hematopoietic stem cell transplantation and found that increased bacterial diversity was associated with decreased mortality associated with GVHD, with an increased number of *Braunschweiger* spp. being significantly associated with decreased mortality in GVHD [59]. Furthermore, rationally selected strains of *Clostridium perfringens* with high butyric acid production, which produce butyrate, protect the intestinal epithelium and reduce the severity of GVHD, thus improving survival [60]. Therefore, maintaining the stability of intestinal microecology and protecting the integrity of the intestinal mucosa is beneficial in reducing the incidence of GVHD during transplantation therapy and improving patient survival.

CAR-T is a major advance in cancer therapy with targeted and low toxicity for a variety of malignant hematologic tumors including lymphoma and leukemia [61, 62]. A recent study in children showed that infections in 40% of them occurred within the first few days after CAR-T treatment, and in about half of the children within 3 months after CAR-T treatment. Bacteria accounted for half of the infectious factors, especially *Escherichia coli*, *Klebsiella*, *Enterococcus* and *Staphylococcus* [63]. In adult patients, the occurrence of infections was more common within 2 months after CAR-T treatment, and bacteria were also the main causative factor for infections. Interestingly, intestinal infections accounted for the vast majority of infectious events [64]. This demonstrates the disruption that CAR-T therapy can cause to the intestinal microecological balance. However, Luu et al. found that the gut flora metabolites SCFAs valerate and butyrate could improve the efficacy of CAR-T by increasing the expression of CTL-related effector molecules in ROR1-specific CAR-T cells [65]. Up to now, there are fewer studies on the role of gut microbes in CAR-T therapies, which deserve further exploration by relevant researchers because of their large application potential.

6. Conclusion and prospect

Leukemia is a malignant disease with complex etiology and pathogenesis. In this paper, we have described that intestinal microecology can influence leukemogenesis and development through immunity, inflammation, metabolites of the flora, metabolic processes of the body, and genetic mutations in many ways. When leukemia patients are treated with chemotherapy, Allo-HSCT or CAR-T, gut microbiota diversity and/or abundance is affected, and gut microbes can also influence the efficacy of treatment through feedback regulation, in addition to the use of probiotics can improve the side effects associated with leukemia treatment. Future studies or further observations using corresponding basic experiments and clinical trials may provide new directions and ideas for microbial effects on adjuvant leukemia therapy.

References

- [1] SUNG H, FERLAY J, SIEGEL R L, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries [J]. *CA Cancer J Clin*, 2021, 71(3): 209-49.
- [2] ZHENG R, ZHANG S, ZENG H, et al. Cancer incidence and mortality in China, 2016 [J]. *Journal of the National Cancer Center*, 2022.
- [3] WANG J, KURILSHIKOV A, RADJABZADEH D, et al. Meta-analysis of human genome-microbiome association studies: the MiBioGen consortium initiative [J]. *Microbiome*, 2018, 6(1): 101.
- [4] HOEK M, MERKS R M H. Emergence of microbial diversity due to cross-feeding interactions in a spatial model of gut microbial metabolism [J]. *BMC Syst Biol*, 2017, 11(1): 56.
- [5] NICHOLSON J K, HOLMES E, KINROSS J, et al. Host-gut microbiota metabolic interactions [J]. *Science*, 2012, 336(6086): 1262-7.
- [6] EATON K, PIRANI A, SNITKIN E S. Replication Study: Intestinal inflammation targets cancer-inducing activity of the microbiota [J]. *Elife*, 2018, 7.
- [7] YUAN X, CHANG C, CHEN X, et al. Emerging trends and focus of human gastrointestinal microbiome research from 2010-2021: a visualized study [J]. *J Transl Med*, 2021, 19(1): 327.
- [8] PITLIK S D, KOREN O. How holobionts get sick-toward a unifying scheme of disease [J]. *Microbiome*, 2017, 5(1): 64.
- [9] BARKO P C, MCMICHAEL M A, SWANSON K S, et al. The Gastrointestinal Microbiome: A Review [J]. *J Vet Intern Med*, 2018, 32(1): 9-25.
- [10] WIRBEL J, PYL P T, KARTAL E, et al. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer [J]. *Nat Med*, 2019, 25(4): 679-89.
- [11] RIQUELME E, ZHANG Y, ZHANG L, et al. Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes [J]. *Cell*, 2019, 178(4): 795-806.e12.
- [12] JIA X, LU S, ZENG Z, et al. Characterization of Gut Microbiota, Bile Acid Metabolism, and Cytokines in Intrahepatic Cholangiocarcinoma [J]. *Hepatology*, 2020, 71(3): 893-906.
- [13] BOBIN-DUBIGEON C, LUU H T, LEUILLET S, et al. Faecal Microbiota Composition Varies between Patients with Breast Cancer and Healthy Women: A Comparative Case-Control Study [J]. *Nutrients*, 2021, 13(8).
- [14] REN Z, LI A, JIANG J, et al. Gut microbiome analysis as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma [J]. *Gut*, 2019, 68(6): 1014-23.
- [15] AGANS R, GORDON A, KRAMER D L, et al. Dietary Fatty Acids Sustain the Growth of the Human Gut Microbiota [J]. *Appl Environ Microbiol*, 2018, 84(21).
- [16] ZELANTE T, IANNITTI R G, CUNHA C, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22 [J]. *Immunity*, 2013, 39(2): 372-85.
- [17] COSOVANU C, NEUMANN C. The Many Functions of Foxp3(+) Regulatory T Cells in the Intestine [J]. *Front Immunol*, 2020, 11: 600973.

- [18] SEFIK E, GEVA-ZATORSKY N, OH S, et al. MUCOSAL IMMUNOLOGY. Individual intestinal symbionts induce a distinct population of ROR γ^+ regulatory T cells [J]. *Science*, 2015, 349(6251): 993-7.
- [19] SU X, ZHANG M, QI H, et al. Gut microbiota-derived metabolite 3-idoleacetic acid together with LPS induces IL-35(+) B cell generation [J]. *Microbiome*, 2022, 10(1): 13.
- [20] SUN M, WU W, CHEN L, et al. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis [J]. *Nat Commun*, 2018, 9(1): 3555.
- [21] SMITH P M, HOWITT M R, PANIKOV N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis [J]. *Science*, 2013, 341(6145): 569-73.
- [22] PARK J, KIM M, KANG S G, et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway [J]. *Mucosal Immunol*, 2015, 8(1): 80-93.
- [23] YANG W, YU T, HUANG X, et al. Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity [J]. *Nat Commun*, 2020, 11(1): 4457.
- [24] ABE Y, KONOPLEVA M. Leukemia Stem Cells Microenvironment [J]. *Adv Exp Med Biol*, 2017, 1041: 19-32.
- [25] HONDA K, LITTMAN D R. The microbiota in adaptive immune homeostasis and disease [J]. *Nature*, 2016, 535(7610): 75-84.
- [26] LEVY M, KOLODZIEJCZYK A A, THAISS C A, et al. Dysbiosis and the immune system [J]. *Nat Rev Immunol*, 2017, 17(4): 219-32.
- [27] MANTIS N J, ROL N, CORTHÉSY B. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut [J]. *Mucosal Immunol*, 2011, 4(6): 603-11.
- [28] Xia Ting, Li Yu, Zhang Chenwei, et al. Research progress on the effect of intestinal flora on leukemia [J]. *Chinese Pharmacology Bulletin*, 2020, 36(05): 593-6.
- [29] ZAHARAN A M, SHIBL A, RAYAN A, et al. Increase in polymorphonuclear myeloid-derived suppressor cells and regulatory T-cells in children with B-cell acute lymphoblastic leukemia [J]. *Sci Rep*, 2021, 11(1): 15039.
- [30] TANG C, DING R, SUN J, et al. The impacts of natural polysaccharides on intestinal microbiota and immune responses - a review [J]. *Food Funct*, 2019, 10(5): 2290-312.
- [31] LIU R T, WANG X X, SUN J R, et al. Correlations of IL-6 and IL-10 gene polymorphisms with childhood acute lymphoblastic leukemia [J]. *Eur Rev Med Pharmacol Sci*, 2020, 24(15): 8048-56.
- [32] IIDA N, DZUTSEV A, STEWART C A, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment [J]. *Science*, 2013, 342(6161): 967-70.
- [33] COLOTTA F, ALLAVENA P, SICA A, et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability [J]. *Carcinogenesis*, 2009, 30(7): 1073-81.
- [34] RAMOS G P, PAPADAKIS K A. Mechanisms of Disease: Inflammatory Bowel Diseases [J]. *Mayo Clin Proc*, 2019, 94(1): 155-65.
- [35] TILG H, ZMORA N, ADOLPH T E, et al. The intestinal microbiota fuelling metabolic inflammation [J]. *Nat Rev Immunol*, 2020, 20(1): 40-54.
- [36] GERLOFF D, GRUNDLER R, WURM A A, et al. NF- κ B/STAT5/miR-155 network targets PU.1 in FLT3-ITD-driven acute myeloid leukemia [J]. *Leukemia*, 2015, 29(3): 535-47.
- [37] ZHANG Y, YU X, LIN D, et al. Propiece IL-1 α facilitates the growth of acute T-lymphocytic leukemia cells through the activation of NF- κ B and SP1 [J]. *Oncotarget*, 2017, 8(9): 15677-88.
- [38] LEE S, KIM H, YOU G, et al. Bone marrow CX3CR1 $^+$ mononuclear cells relay a systemic microbiota signal to control hematopoietic progenitors in mice [J]. *Blood*, 2019, 134(16): 1312-22.
- [39] RODRÍGUEZ-HERNÁNDEZ G, HAUER J, MARTÍN-LORENZO A, et al. Infection Exposure Promotes ETV6-RUNX1 Precursor B-cell Leukemia via Impaired H3K4 Demethylases [J]. *Cancer Res*, 2017, 77(16): 4365-77.
- [40] ØSTGÅRD L S G, NØRGAARD M, PEDERSEN L, et al. Autoimmune diseases, infections, use of antibiotics and the risk of acute myeloid leukaemia: a national population-based case-control study [J]. *Br J Haematol*, 2018, 181(2): 205-14.

- [41] GREAVES M. A causal mechanism for childhood acute lymphoblastic leukaemia [J]. *Nat Rev Cancer*, 2018, 18(8): 471-84.
- [42] MCDONALD T A, HOLLAND N T, SKIBOLA C, et al. Hypothesis: phenol and hydroquinone derived mainly from diet and gastrointestinal flora activity are causal factors in leukemia [J]. *Leukemia*, 2001, 15(1): 10-20.
- [43] SONG Y, GYARMATI P. Microbiota changes in a pediatric acute lymphocytic leukemia mouse model [J]. *Microbiologyopen*, 2020, 9(3): e982.
- [44] STRICK R, STRISSEL P L, BORGERS S, et al. Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia [J]. *Proc Natl Acad Sci U S A*, 2000, 97(9): 4790-5.
- [45] SCHULTHEISS J, PANDEY S, CAPITANI M, et al. The Short Chain Fatty Acid Butyrate Imprints an Antimicrobial Program in Macrophages [J]. *Immunity*, 2019, 50(2): 432-45.e7.
- [46] NAKKARACH A, FOO H L, SONG A A, et al. Anti-cancer and anti-inflammatory effects elicited by short chain fatty acids produced by *Escherichia coli* isolated from healthy human gut microbiota [J]. *Microb Cell Fact*, 2021, 20(1): 36.
- [47] BASEN-ENGQUIST K, CHANG M. Obesity and cancer risk: recent review and evidence [J]. *Curr Oncol Rep*, 2011, 13(1): 71-6.
- [48] CHEN W-L, WANG Y-Y, ZHAO A, et al. Enhanced Fructose Utilization Mediated by SLC2A5 Is a Unique Metabolic Feature of Acute Myeloid Leukemia with Therapeutic Potential [J]. *Cancer Cell*, 2016, 30(5): 779-91.
- [49] YE H, ADANE B, KHAN N, et al. Subversion of Systemic Glucose Metabolism as a Mechanism to Support the Growth of Leukemia Cells [J]. *Cancer Cell*, 2018, 34(4): 659-73.e6.
- [50] XU Y P, LV L, LIU Y, et al. Tumor suppressor TET2 promotes cancer immunity and immunotherapy efficacy [J]. *J Clin Invest*, 2019, 129(10): 4316-31.
- [51] JIANG S. Tet2 at the interface between cancer and immunity [J]. *Commun Biol*, 2020, 3(1): 667.
- [52] MEISEL M, HINTERLEITNER R, PACIS A, et al. Microbial signals drive pre-leukaemic myeloproliferation in a Tet2-deficient host [J]. *Nature*, 2018, 557(7706): 580-4.
- [53] ZHOU B, XIA X, WANG P, et al. Induction and Amelioration of Methotrexate-Induced Gastrointestinal Toxicity are Related to Immune Response and Gut Microbiota [J]. *EBioMedicine*, 2018, 33: 122-33.
- [54] LIU T, WU Y, WANG L, et al. A More Robust Gut Microbiota in Calorie-Restricted Mice Is Associated with Attenuated Intestinal Injury Caused by the Chemotherapy Drug Cyclophosphamide [J]. *mBio*, 2019, 10(2).
- [55] REYNA-FIGUEROA J, BARRÓN-CALVILLO E, GARCÍA-PARRA C, et al. Probiotic Supplementation Decreases Chemotherapy-induced Gastrointestinal Side Effects in Patients With Acute Leukemia [J]. *J Pediatr Hematol Oncol*, 2019, 41(6): 468-72.
- [56] LEE C J, SAVANI B N, MOHTY M, et al. Post-remission strategies for the prevention of relapse following allogeneic hematopoietic cell transplantation for high-risk acute myeloid leukemia: expert review from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation [J]. *Bone Marrow Transplant*, 2019, 54(4): 519-30.
- [57] FREDRICKS D N. The gut microbiota and graft-versus-host disease [J]. *J Clin Invest*, 2019, 129(5): 1808-17.
- [58] ERIGUCHI Y, TAKASHIMA S, OKA H, et al. Graft-versus-host disease disrupts intestinal microbial ecology by inhibiting Paneth cell production of α -defensins [J]. *Blood*, 2012, 120(1): 223-31.
- [59] JENQ R R, TAUR Y, DEVLIN S M, et al. Intestinal *Blautia* Is Associated with Reduced Death from Graft-versus-Host Disease [J]. *Biol Blood Marrow Transplant*, 2015, 21(8): 1373-83.
- [60] MATHEWSON N D, JENQ R, MATHEW A V, et al. Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease [J]. *Nat Immunol*, 2016, 17(5): 505-13.
- [61] ABID M B, SHAH N N, MAATMAN T C, et al. Gut microbiome and CAR-T therapy [J]. *Exp Hematol Oncol*, 2019, 8: 31.
- [62] NAIR R, WESTIN J. CAR T-Cells [J]. *Adv Exp Med Biol*, 2020, 1244: 215-33.

- [63] VORA S B, WAGHMARE A, ENGLUND J A, et al. Infectious Complications Following CD19 Chimeric Antigen Receptor T-cell Therapy for Children, Adolescents, and Young Adults [J]. Open Forum Infect Dis, 2020, 7(5): ofaa121.
- [64] WUDHIKARN K, PALOMBA M L, PENNISI M, et al. Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma [J]. Blood Cancer J, 2020, 10(8): 79.
- [65] LUU M, RIESTER Z, BALDRICH A, et al. Microbial short-chain fatty acids modulate CD8(+) T cell responses and improve adoptive immunotherapy for cancer [J]. Nature communications, 2021, 12(1): 4077-.