Blood Science

Gut microbiota plays pivotal roles in benign and malignant hematopoiesis

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Abstract

Accumulated evidence emerges that dynamic changes in human gut microbiota and microbial metabolites can alter the ecological balance of symbiotic hosts. The gut microbiota plays a role in various diseases through different mechanisms. More and more attention has been paid to the effects that human microbiota extends beyond the gut. This review summarized the current understanding of the roles that gut microbiota plays in hematopoietic regulation and the occurrence and development of benign and malignant hematologic diseases. The progress of the application of microbiota in treatment was discussed in order to provide new insights into clinical diagnosis and treatment in the future.

Key Words: Fecal microbiota transplantation; Graft-versus-host disease; Gut microbiota; Hematologic diseases; Hematopoietic stem cells

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1. INTRODUCTION

The microbial community inhabiting the human body is composed of bacteria, archaea, fungi, protozoa, and viruses. However, bacteria account for 3 orders of magnitude more than other microorganisms.[1] Gastrointestinal microbiota is the largest microbial ecosystem in the human body and has been most extensively studied. The bacteria in mammalian gut microbiota mainly consist of 4 phyla: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*, which together account for over 95% of the total bacteria.[2] There is no "gold standard" for evaluating healthy gut microbiota, however, it is a consensus that the healthy gut microbiota has a high degree of taxonomic diversity, a high degree of gene richness, and a stable functional microbial core group.[3]

The presence of detrimental pathogenic bacteria or the absence of beneficial bacteria in gut microbiota is called gut dysbiosis. Changes in microbial diversity and the abundance of individual species can destroy the microbial balance and may lead to a variety of diseases. It has been demonstrated that many diseases including diabetes, obesity, neurodegenerative diseases, hypertension, multiple systemic infections, and the occurrence of various tumors, are related to the gut microbiota.[3–5] In the hematological system, gut microbiota dysbiosis can affect hematopoiesis, lead to the occurrence of various hematological diseases, and affect the consequence of disease treatment.

Understanding the mechanism and regulation of gut microbiota and hematology is helpful in exploring the new pathogenesis of hematological diseases and provides potential therapeutic targets. In addition, it probably provides a new noninvasive method for monitoring the prognosis of patients. In this article, we will review and prospectively discuss the relationship

between gut microbiota and hematopoiesis and hematological diseases.

2. GUT MICROBIOTA AND HEMATOPOIETIC SYSTEM

Hematopoietic stem and progenitor cells (HSPCs) are crucial for maintaining hematopoietic homeostasis in bone marrow. Previous studies focused on the composition and functional regulation of bone marrow microenvironment, which is important for hematopoiesis.[6] However, it has been demonstrated that gut microbiota also plays an essential role in regulating the hematopoietic system. We reviewed the potential mechanisms in this field in Figure 1.

Several studies have elucidated the important roles of gut microbiota in mature blood cell production. In germ-free (GF) mice, the gut microbiota is entirely depleted. Compared with specific-pathogen-free (SPF) mice, the smaller HSPCs population and abnormal splenic myeloid counts were observed in GF mice.[7,8] During steady-state conditions, the gut microbiota facilitate the maintenance of HSCs. However, the absence of commensal microbes results in defects in the innate immune cell population, including neutrophils, monocytes, and macrophages.[7] Similarly, the depletion of gut microbiota in adult mice treated with antibiotics has a suppressive effect on hematopoiesis.[7,9–11] Josefsdottir et al[9] found that depletion of the gut microbiota disrupts the basal Stat1 signal and changes T-cell homeostasis, leading to impaired hematopoietic progenitor maintenance and granulocyte maturation. However, this inhibitory effect is reversible.[9] Therefore, more attention should be paid to preserving the gut microbiome during treatment to reduce the incidence of antibiotic-related bone marrow suppression.

Zhang et al[12] found that short-chain fatty acid (SCFA) butyrate, produced by gut microbiota, can promote macrophage-mediated erythrophagocytosis, thereby regulating iron metabolism in the bone marrow to control HSC self-renewal and differentiation during early stages of hematopoietic system reconstruction. Mechanistically, gut microbiota depletion in mice regulated macrophage function and impaired erythrophagocytosis via SCFA. Restricting iron intake or consuming macrophages in the bone marrow enhanced HSC self-renewal and limited HSPC differentiation. The microbiota-macrophage-iron axis plays a critical role in HSC fate decision to maintain hematopoietic homeostasis. Lee et al[13] found that lactate produced by gut microbiota stimulates bone marrow stromal cells to secrete hematopoietic cytokines in a G protein-coupled receptor 81 (Gpr81)–dependent manner, promoting hematopoiesis and erythrocyte generation. Therefore, oral intake of probiotics may help restore blood cell generation and provide potential therapeutic strategies for patients with chronic anemia. Yan et al[14] found that the metabolites of gut microbiota can promote hematopoiesis and rescue hematopoietic defects induced by antibiotics through activating type I interferon (IFN) and signal transducer and activator of transcription 1 (STAT1) signaling. This study provided a therapeutic strategy to ameliorate antibiotic-induced bone marrow suppression and cytopenia.

In addition to these common metabolites, the lipopolysaccharides (LPS) derived from gut microbiota can be directly recognized by Toll-like receptor 4 (TLR4) on the HSC, and activate the inflammatory response through the TLR4-TRIF-ROS-p38 signaling axis. LPS stimulation resulted in the proliferation of dormant HSC directly via TLR4 and impaired HSC self-renewal and regenerative capacity.[15] Iwamura et al[8] found that ligand from gut microbiota was sensed by NOD1 in bone marrow mesenchymal stromal cells, and then induced expression of several hematopoietic cytokines (including stem cell factor, interleukin (IL)-7, IL-6, TPO, Flt3L), revealing that NOD1 signaling in mesenchymal stromal cells serves as an essential role in maintaining steady hematopoiesis. Another research revealed that microbiota-derived molecules, including bacterial DNA, can reach bone marrow through blood circulation and are sensed by CX3CR1+ mononuclear cells via endolysosomal TLRs. Microbiota-derived molecules promote the production of inflammatory cytokines, resulting in the expansion of hematopoietic progenitor cells and the potential differentiation of the myeloid lineage.[16]

Aging induces a significant alternation of gut microbiota composition and declines the diversity in humans.[17] The shifted gut microbiota impaired systemic hematopoiesis. Thevaranjan et al[18] found that age-related microbial dysbiosis resulted in increased intestinal permeability, which promoted microbial products to enter the bloodstream of aged mice. The leaked microbial products further elevated the levels of inflammatory cytokines. Macrophages exposed to chronic inflammation had a poor ability to kill bacteria and produced more inflammatory cytokines, which contributed to the inflammatory state of the aged host. Kovtonyuk et al[19] demonstrated that during aging, gut microbial compounds leak into the circulation, thus inducing a myeloid-bias differentiation of HSCs. Furthermore, they revealed that the IL-1 receptor is important for the expression of inflammation genes in aged HSCs by using IL-1 receptor 1 knockout and GF mice. Despite IL-1 inhibition decreased HSC myeloid differentiation skewing, it failed to restore the engraftment ability to the level of HSC from young donor mice. Our recent study found that fecal microbiota transplantation (FMT) from young mice to aged mice rejuvenated aged HSCs with enhanced HSC repopulation capacity.[20] The mitigated inflammatory signals and increased FoxO signaling pathway were observed in HSC from FMT receipt mice. In this process, *Lachnospiraceae* and tryptophan-related metabolites played an important role in the recovery of hematopoiesis.

Current studies indicate that microbial products, including LPS, and NOD1 ligands, are important for hematopoiesis and aging through activating inflammation signal pathways. Meanwhile, the metabolites produced by gut microbiota, such
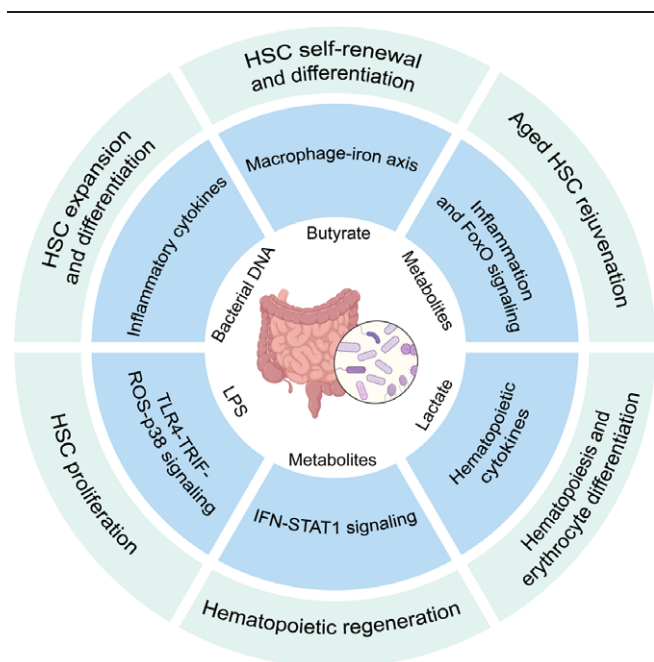

Figure 1. Mechanisms of gut microbiota in the regulation of hematopoiesis. FoxO = Forkhead box O, HSC = hematopoietic stem cell, IFN = interferon, LPS = lipopolysaccharides, ROS = reactive oxygen species, STAT = signal transducer and activator of transcription, TLR4 = Toll-like receptor 4, TRIF = TIR domain -containing adaptor inducing interferon-b.

as SCFA, also play an essential role in hematopoietic regulation. Although these studies provide new insights to maintain the function of HSPCs, the detailed mechanisms of the impact of gut microbiota on hematopoiesis are still unclear. Further experiments will be warranted to elucidate the connection between gut microbiota and hematopoietic system.

3. GUT MICROBIOTA AND HEMATOLOGICAL MALIGNANCIES

Hematological malignancies refer to a group of malignant tumors originating from the hematopoietic system, including leukemia, lymphoma, and myeloma. They have the characteristics of increasing incidence, high malignancy, complex treatment, and poor prognosis, and have become a severe challenge in the field of public health. Researchers have uncovered the alternation of gut microbiota during the development of hematological malignancies in decades years (**Fig. 2**).

3.1. Leukemia

According to the differentiation and course of leukemia, it can be divided into acute leukemia and chronic leukemia. According to the affected blood cells, it can be divided into lymphocytic leukemia and myeloid leukemia. In recent years, many studies have revealed the role of gut microbiota in the course, treatment, and prognosis of leukemia.

3.1.1. Acute lymphoblastic leukemia (ALL) The composition of gut microbiota in ALL patients has been identified. Liu et al[21] found that the composition of gut microbiota in children with ALL was different from that of healthy children by analyzing fecal samples from children with ALL and healthy children. Compared to healthy control, the abundance of *Roseburia faecis*, *Edwardsiella tarda*, and *Fusobacterium naviforme* decreased in ALL patients, and the abundance of

Bacteroides clarus increased. Similarly, a study found that in children with ALL, their gut microbiota were enriched with bacteria belonging to the Bacteroidetes phylum, and after chemotherapy, the proportion may decrease.[22] Furthermore, the characteristic composition of gut microbiota can be used to predict infections during ALL treatment.[23] In a cohort of 199 children with ALL, researchers found that a higher abundance of *Bacteroides* at baseline predicted the occurrence of febrile neutropenia. Meanwhile, the patients whose gut microbiota was dominated by *Enterococcaceae* and *Streptococcaceae* during treatment had an increased risk of infectious complications, which is also demonstrated by another research that overgrowth of Enterococci may characterize the patient who has a higher risk of intestinal mucositis during chemotherapy.[24] Liu et al[25] also revealed that the different composition of gut microbiota between patients with ALL and healthy individuals was associated with the occurrence of pneumonia during chemotherapy. Another study found that the microbiota diversity and richness of the ALL patient decreased compared to their healthy sibling controls at diagnosis and during chemotherapy. The composition of gut microbiota tended to be stable after 1-year post-chemotherapy; however, their abundances were still altered, indicating that chemotherapy may have long-term adverse effects on the resident gut microbiota.[26]

3.1.2. Acute myeloid leukemia (AML) A recent study revealed that gut microbiota dysbiosis accelerates the progress of AML in murine models, and the intestinal barrier is damaged in AML mice. The treatment of butyrate derived from gut microbiota and FMT inhibits the progress of AML. The damaged intestinal barrier in AML mice, which could be repaired by butyrate, exacerbates leukemia progression through increasing LPS absorption.[27]

A recent study showed that the ratio of Firmicutes to Bacteroidetes increased in AML patients at the phylum level, indicating the presence of dysbiosis.[28] Galloway-Pena et al[29] found that the baseline α-diversity of fecal samples in AML
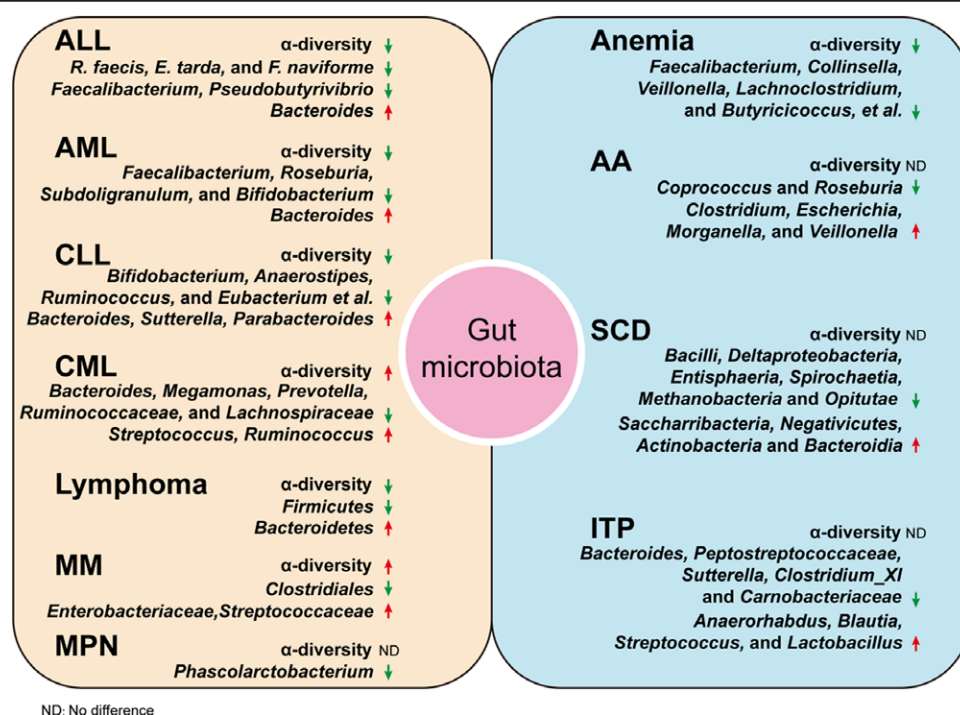

Figure 2. Alteration of gut microbiota in hematopoietic diseases. AA = aplastic anemia, ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CLL = chronic lymphocytic leukemia, CML = chronic myeloid leukemia, ITP = immune thrombocytopenia, MM = multiple myeloma, MPN = myeloproliferative neoplasms, SCD = sickle cell disease.

patients who developed infections during induction chemotherapy was significantly lower than those who did not. Meanwhile, the diversity of gut microbiota in patients gradually decreased during chemotherapy. In subsequent studies, they revealed that the patients with higher Shannon diversity of stool and higher abundance of *Porphyromonadaceae* at the beginning of induction chemotherapy were accompanied by a decreased probability of infection during neutropenia. These results suggested that the evaluation of gut microbiome could assist with infectious risk stratification and optimized treatment of antibiotics during induction chemotherapy could decrease infections in AML patients.[30]

In AML patients with febrile neutropenia, the gut microbiota diversity decreased after initial chemotherapy and remained unchanged after bone marrow reconstruction.[31] Therefore, detecting the gut microbiota can help evaluate the risk of infection in AML patients during treatment, and improved antibiotic administration during induction chemotherapy could reduce the incidence of infectious complications in AML patients.

In terms of treatment, studies have found that supplementing probiotics is beneficial in preventing gastrointestinal side effects induced by chemotherapy. Reyna-Figueroa et al[32] conducted a randomized trial of oral supplementation with *Lactobacillus rhamnosus* GG (LGG) in 60 children with ALL and AML receiving chemotherapy and found that the incidence of gastrointestinal adverse reactions such as diarrhea, nausea, and vomiting decreased after supplementation with LGG. Malard et al[33] found that autologous fecal microbiota transfer (AFMT) can restore gut microbiota destroyed by intensive chemotherapy and antibiotic treatment in AML patients, restoring the α-diversity index to the initial mean level.

3.1.3. Chronic lymphocytic leukemia (CLL) Recently, Faitova et al[34] conducted a study on 10 CLL patients and found that the gut microbiota diversity of CLL patients was lower than that of healthy controls, and the enrichment of SCFA-producing bacterial taxa decreased. At genus level, *Bacteroides*, *Sutterella*, and *Parabacteroides* were found to be over presented in CLL cohort relative to the average microbiome. On the contrary, a group of taxa, including *Bifidobacterium*, *Anaerostipes*, and 9 other bacterial genera, were identified to be underrepresented among CLL patients. Consistently, Kawari et al[35] also found a reduced diversity of gut microbiota in CLL patients compared to healthy controls. Furthermore, increased *Firmicutes* and reduced *Bacteriodetes* were observed in CLL patients. Another study found that the gut microbiota of CLL patients treated with B cell receptor (BCR) inhibitors who met the clinical response criteria had a higher number of bacteria from the class *Bacteroidia* and the order *Bacteroidales*, they also noted an inversion in the *Firmicutes* and *Bacteroidetes* ratio in the patients who undergo adverse effects such as diarrhea.[36]

3.1.4. Chronic myeloid leukemia (CML) Yu et al[37] confirmed the changes in gut microbiota in CML patients through 16S RNA sequencing of fecal samples and found that microbiota α-diversity and the abundance of *Streptococcus* increased in CML populations, suggesting further research focused on the role of *Streptococcus* in myeloid leukemia development is essential. LPS is found to induce inflammation in K562 (CML) cell line, causing the elevation of a series of inflammatory cytokines including IL-10, IL-6, and tumor necrosis factor (TNF)-α, which implies the role of immune system in CML.[38] Based on reports of immune system dysregulation during CML development and the increasing attention to the relationship between the immune system and gut microbiota, Pagani et al[39] considered that the sustained changes in gut microbiota in CML patients may affect the regulation of the immune system and thus influence CML

disease progression and relapse, but more evidence is needed to confirm this hypothesis.

3.2. Lymphoma

Diefenbach et al[40] found that compared to healthy individuals, the *Bacteroidetes* increased and *Firmicutes* decreased in the gut microbiota of patients with B-cell non-Hodgkin lymphoma (B-NHL). Specifically, patients with aggressive lymphomas (like diffuse large B-cell lymphoma) have significantly lower microbiota diversity than those with indolent non-Hodgkin lymphomas. In addition, patients who respond to immunotherapy have higher microbiota diversity before treatment.[40] Cozen et al[41] investigated the fecal microbiota of 13 adolescent/young adult Hodgkin lymphoma (AYAHL) survivors and their co-twin controls and found that the diversity in the fecal microbiota of AYAHL survivors showed modest reductions. The time interval between diagnosis and participation in the study was an average of 22.5 years, indicating that the gut microbiota dysbiosis caused by disease and treatment may have long-term consequences.[41] As for diagnosis, Shi et al[42] found that gut microbiota can serve as noninvasive diagnostic and prognostic biomarkers for natural killer/ T-cell lymphoma (NKTCL), and established the SRI index (*Streptococcus parasanguinis-Romboutsia timonensis* index), a relative abundance ratio of 2 species, to evaluate overall survival (OS) and progression-free survival (PFS) in patients. The SRI index was validated in a cohort of 30 patients, showing that patients with a higher SRI index had significantly worse OS and PFS than those with lower SRI scores and a high SRI index was significantly correlated with poor prognosis factors of NKTCL.

3.3. Multiple myeloma (MM)

MM is a malignant tumor caused by the abnormal proliferation of terminally differentiated plasma cells. Jian et al[43] found that the gut microbial diversity in MM patients was significantly higher than that in healthy individuals due to excessive accumulation of blood urea, and the nitrogen-cycling bacteria, such as *Klebsiella* and *Streptococcus* significantly increased. Using a mouse model, they found that *Klebsiella pneumoniae* promoted the proliferation of myeloma cells and accelerated MM progression via de novo synthesis of L-glutamine in mice, suggesting gut microbiota can also affect MM through bioactive metabolites.[43] Another study observed that the relative abundance of *Eubacterium hallii* and *Faecalibacterium prausnitzii* in MM patients without minimal residual disease (MRD) was higher than those in patients with MRD after induction therapy, indicating that the gut microbiota composition is associated with deep treatment response.[44]

In addition, Calcinotto et al[45] demonstrated that *Prevotella* promotes Th17 cell differentiation and migration to the bone marrow, and accelerates tumor progression in transgenic Vk*MYC mice. IL-17 produced by Th17 cells can induce STAT3 phosphorylation and activate eosinophils, which produce IL-6 and TNF-α, promoting plasma cell proliferation and survival, and playing an important role in the early stage of MM.[45]

3.4. Myeloproliferative neoplasms (MPN)

MPN is a chronic malignant tumor of the blood system, in which inflammation plays an important role in the initiation and progression. A recent study observed that although the microbiota diversity of MPN patients did not significantly differ with healthy controls, the elevated TNF-α in the MPN patients is related to *Veillonella*.[46] *Veillonella* stimulates peripheral blood monocytes to produce TNF-α, highlighting

a potential role in inflammation.[47] However, it is still unclear whether the microbiome change promotes MPN or whether the MPN exaggerated the inflammation response involved in gut microbiota.

4. GUT MICROBIOTA AND NONMALIGNANT HEMATOLOGICAL DISEASES

In recent years, many studies have focused on the role of gut microbiota in nonmalignant hematological diseases such as anemia, aplastic anemia (AA), and immune thrombocytopenia (ITP), and found the changes of gut microbiota in the progress of diseases (**Fig. 2**), providing more evidence to reveal the relationship between gut microbiota ecology and nonmalignant hematological diseases.

4.1. Anemia

Anemia is an important global health issue, but the relationship of anemia with gut microbiota remains unclear. A recent study revealed that the taxonomic composition of gut microbiota from women of childbearing age with iron-deficiency anemia showed significant differences with that from normal controls. At genus level, *Faecalibacterium*, *Collinsella*, and *Veillonella* were decreased in patients.[48] Another study showed that the α-diversity of gut microbiota in patients with chronic disease is significantly lower than that in healthy controls, which is accompanied by the decreased abundances of *Faecalibacterium*, *Lachnoclostridium*, *Lachnospiraceae* NK4A136 group, and *Butyricicoccus* genera.[49] Soriano-Lerma et al[50] demonstrated that iron-deficiency anemia results in intestinal dysbiosis manifested as an increase in SCFA-producing bacteria and SCFA concentration in the colon of rat model. This could be a trade-off mechanism against disease, indicating that supplementation of SCFA or SCFA-producing bacteria may be beneficial to iron-deficiency anemia patients. Iron supplementation therapy is the basic treatment for iron deficiency. However, studies indicate that iron supplementation may have adverse effects on the gut microbiota. Ippolito et al[51] showed that unabsorbed iron in the lower gut of mice fed iron-rich foods can alter the gut microbiota and cause more severe gut diseases, and the change in gut microbiota can further affect iron absorption. Mechanismly, excessive unabsorbed iron participates in Fenton and Haber-Weiss reactions when passing through the gut, which can have detrimental effects on the gut structure. Iron supplementation has negative effects on beneficial bacterial colonization in the gut and leads to a relative increase in pathogenic microorganisms, causing more gut inflammation. The change in gut microbiota composition also affects iron absorption.[52,53] Although there are precise regulatory mechanisms to maintain the dynamic balance between iron and gut microbiota, more large-scale research is needed to optimize iron therapy targeting different anemia patients and reduce therapeutic side effects.

4.2. Aplastic anemia

In severe aplastic anemia (SAA) patients, the abnormalities in both plasma metabolomes and gut microbiota were observed, including the increase of *Clostridium*, *Escherichia*, *Morganella*, and *Veillonella* and the reduction of *Coprococcus* and *Roseburia*. This study suggested that gut microbiota may activate immune response by producing proinflammatory factors.[54] Another study indicated that in SAA patients who received hematopoietic stem cell transplantation (HSCT) or immunosuppressive therapy, the oral microbiota changed significantly after treatment.[55] Zhao et al[56] reported a case of a refractory SAA patient and found that long-term immune responses in SAA patients are related to changes in gut microbiota and chronic inflammation.

4.3. Sickle cell disease (SCD)

The researchers found that SCD patients had a lower proportion of *Firmicutes/Bacteroidetes* in their gut microbiota compared to healthy controls, and there were significant differences in the bacterial classes, orders, and families of 10, 11, and 20 strains, respectively. Similar changes were not observed in the oral microbiota, indicating that SCD patients may have severe intestinal dysbiosis.[57] Another study found that children with SCD have a higher abundance of *Actinobacteria*, however, the difference in gut microbiota was not consistent with the above study at family level.[58] Currently, there have been few studies on the relationship between SCD and gut microbiota, and more sample studies are needed to verify the conclusions.

4.4. Immune thrombocytopenia

Liu et al[59] detected the composition of gut microbiota in ITP patients and found an increased proportion of *Proteobacteria*, *Bacteroidetes*, and *Bacteroidetes/Firmicutes* ratio, a decreased proportion of *Firmicutes* compared with healthy controls. The decreased ratio of *Firmicutes/Bacteroidetes* was characterized in this study, which is consistent with some systemic inflammation. Although there was no significant difference in the diversity of the microbiota, they identified 5 specific bacterial taxa (*Anaerorhabdus*, *Sutterella*, *Peptostreptococcaceae*, *Clostridium_XI*, and *Carnobacteriaceae*) that were significantly associated with ITP, which had the potential to serve as biomarkers for ITP.

Another study found that the gut microbiome of ITP patients was enriched with *Blautia*, *Lactobacillus*, and *Streptococcus* species, and the relative abundance of *Streptococcus anginosus* was increased 35-fold compared to healthy controls. Meanwhile, fecal metabolites, such as fatty acyls and glycerophospholipids, were enriched and strongly correlated with the discrepant gut microbiota. Whereas, the abundance of *Bacteroides* is decreased in ITP patients. In addition, the relative abundance of *Streptococcus anginosus* had a strong negative correlation with platelet counts, suggesting that these bacteria may play an important role in the development of ITP.[60] However, the specific mechanisms by which the gut microbiota influences the disease require further investigation.

Although there have been many studies on the role of the gut microbiome in nonmalignant hematological disorders, the current understanding of the role of the gut microbiome is limited. Therefore, larger experimental studies and further investigation of the specific mechanisms of the gut microbiome are needed to verify the current conclusions.

5. THE ROLE OF THE GUT MICROBIOME IN THE TREATMENT OF HEMATOLOGICAL DISORDERS

There is increasing evidence that the gut microbiota may play an important role in the treatment of malignant blood tumors.[9,61–65] Elucidating the relationship between the gut microbiota and the outcome of various treatments may contribute to preventive and therapeutic interventions for patients with hematological diseases. The related studies are summarized in Table 1.

5.1. Chemotherapy

Conventional chemotherapy drugs can damage the intestinal mucosa and alter the composition of the gut microbiome. It was reported that cyclophosphamide, one of several important anti-cancer drugs, altered the composition of microbiota in the small intestine and promoted the translocations of selected species of gram-positive bacteria into secondary lymphoid organs in mouse models.[66] These bacteria are helpful

Related studies of gut microbiota in the treatment of hematopoietic diseases.

Treatment	Microbiota feature	Outcome
Chemotherapy	Cyclophosphamide altered the composition of microbiota and promoted the translocations of specific gram-positive bacteria	Stimulate the generation of Th17 cells and memory Th1 immune response
	Intensive treatment decreased the diversity of gut microbiota and reduced urinary Hippurate and fecal bacterial amino acid	Impair gut barrier function and body weight loss in AML patients
	Mercaptopurine treatment upregulated relative abundance of f_Lachnospiraceae.g_ASF356 and f_Peptococcaceae.g_uncultured, increased levels of acetate, propionate, and butyrate	Decrease the level of IL-6 and TNF-α and restored the intestinal microbiome dysbiosis in ALL murine model
Immunotherapy	High abundance of *Bifidobacterium*, *Leuconostoc*, *Stenotrophomonas*, and *Staphylococcus*	Occurrence of severe cytokine release syndrome in MM patients with CAR-T therapy
	Pentanoate and butyrate	Enhancement of the anti-tumor activity of CTLs and CAR-T cells
Allo-HSCT	Decrease in microbiota diversity and increase in specific bacterial groups such as *Enterococcus*, *Streptococcus*, and *Lactobacillus*	Accompanied by an increased incidence of GVHD and a decreased transplant survival rate
	Expansion of *Lactobacillales*	Associated with GVHD development
	Decline in *Clostridia*	Development of GVHD
	Microbiome depletion caused by broad-spectrum antibiotics	Development of GVHD
	Prolonged gut microbial alterations	Development and exacerbation of late complications in post-transplant survivors
	Supplementation of butyrate salts and indole components	Alleviate the severity of GVHD and improve transplant survival
	Bile acid salts	Alleviate GVHD reactions
	Dietary lactose deprivation	Improve the severity of GVHD
Novel treatments	Fecal microbiota transplantation	Alleviate post-transplant GVHD
	Intestinal nutrition supplementation	Restore the diversity of gut microbiota and increase SCFA-producing bacteria

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CAR-T = chimeric antigen receptor T-cell therapy, CTL = cytotoxic T lymphocyte, GVHD = graft-versus-host disease, HSCT = hematopoietic stem cell transplantation, IL = interleukin, MM = multiple myeloma, SCFA = short-chain fatty acid, TNF = tumor necrosis factor.

to stimulate the generation of T helper 17 cells and memory Th1 immune response. However, in GF mice or gram-positive bacteria depleted mice, the Th17 response is reduced followed by the resistance of tumors to cyclophosphamide. For AML patients, the intensive treatment impaired the gut barrier and changed the composition of gut microbiota, which was characterized by a loss of diversity. The analysis of metabolites showed that the content of urinary Hippurate and fecal bacterial amino acid metabolites was reduced.[67] In the ALL murine model, mercaptopurine (6-MP) treatment decreased the level of IL-6 and TNF-α and restored the intestinal microbiome dysbiosis. The levels of acetate, propionate, and butyrate were upregulated in the cecum, that in accordance with the upregulated relative abundance of f_Lachnospiraceae.g_ASF356 and f_Peptococcaceae.g_uncultured.[68]

In addition, studies have found that the efficacy of chemotherapy drugs in half of the participants is influenced by the gut microbiota, most likely via enzymatic modifications. Lehouritis et al[69] examined the potential effects of bacteria on the efficacy of chemotherapy drugs and found that the efficacy of some drugs was inhibited by certain bacteria, while the same bacteria improved the efficacy of other drugs. Complete symbiotic microbial flora may be necessary for the treatment of malignant hematologic diseases. Furthermore, understanding the interrelationship between gut microbiota and drug metabolism can help develop more personalized treatment strategies.

5.2. Immunotherapy

In terms of immunotherapy for malignant hematologic diseases, chimeric antigen receptor T-cell therapy (CAR-T therapy) has gradually become a frontline treatment. A recent study found that the Shannon index of gut microbiota decreases after CAR-T therapy and is associated with decreased CAR-T efficacy. Hu et al[64] revealed there were significant differences in the abundance of *Bifidobacterium*, *Prevotella*, *Sutterella*, and *Collinsella* between MM patients in partial remission and those in complete remission. The CAR-T cell therapy-related severe cytokine release syndrome occurred in the MM patients with a higher abundance of *Bifidobacterium*, *Leuconostoc*, *Stenotrophomonas*, and *Staphylococcus*, demonstrating that

gut microbiota alterations were associated with severe cytokine release syndrome. In addition to changes in gut microbiota diversity, the research investigated that SCFA, including butyrate and pentanoate, can increase the anti-tumor activity of cytotoxic T cells and CAR-T cells.[65]

Although personalized regulation of gut microbiota to enhance anti-tumor treatment has not yet been achieved, it is necessary to maintain gut microbiota diversity and beneficial bacterial proportions to enhance the therapeutic effects of CAR-T and reduce side effects. Gut microbiota is expected to become a breakthrough in the future treatment of malignant hematologic tumors.

5.3. HSCT and graft-versus-host disease

HSCT is a common therapy to treat malignant tumors of the hematopoietic system. In the process of allogeneic hematopoietic stem cell transplantation (allo-HSCT), the presence of graft-versus-host disease (GVHD) leads to a higher transplant-related mortality rate, resulting in the limitation of its application. As the gut is one of the major affected organs in GVHD, many studies have been conducted on the role of the intestinal microbiota in GVHD.

Several studies revealed that the gut microbiota of patients with allo-HSCT treatment changes. These changes mainly involve a decrease in microbiota diversity and an increase in specific bacterial groups such as *Enterococcus*, *Streptococcus*, and *Lactobacillus*, as well as a reduction in bacteria-producing butyrate, such as *Clostridiales*. The microbiota changes are accompanied by an increased incidence of GVHD and a decreased transplant survival rate. In a murine model of GVHD, it was observed that the overall diversity of gut microbiota was lost with the expansion of Lactobacillales and reduction of Clostridiales. However, eliminating Lactobacillales from the flora of mice before BMT aggravated GVHD.[70] Simms-Waldrip et al[71] uncovered that pediatric HSCT patients who developed GVHD showed a significant decline in gut anti-inflammatory Clostridia compared with those without GVHD. These alterations in the microbiota may be related to pre-transplant conditioning undergone by the patients.[72–74] Jorgensen et al[75] found species richness, α-diversity, and gene richness of

bacteria decreased in the patients' feces after transplantation. The most significant reduction was observed in patients who underwent myeloablative conditioning before transplantation, accompanied by a decrease in bacterial metabolic function.[75] Furthermore, antibiotic treatment and dietary changes may also participate in the development of GVHD by affecting the changes in gut microbiota.[74,76] Shouval et al[77] revealed a correlation between the degree of pre-transplant conditioning and the level of changes in the intestinal microbiota after transplantation. Recent studies demonstrated that various interventions before and after transplantation disrupt the balance of the intestinal microbiota, which is non-self-limiting and cannot be repaired by the body itself. The disrupted balance of gut microbiota could persist for a long period after transplantation.[78,79]

More and more evidence suggests that the metabolites of gut microbiota play a crucial role in the occurrence and progression of GVHD. The bacterial metabolites, such as butyrate and propionate, are essential for immunology regulation. The reduction of SCFA and butyrate-producing bacterial species can usually be observed in samples after transplantation.[80,81] Similarly to SCFAs, metabolites from amino acids such as indole can maintain intestinal barrier function. Supplementation of butyrate salts and indole components for post-transplant patients can improve the severity of GVHD and transplant survival. Bile acid salts, which are influenced by gut microbiota composition, also contribute to alleviating GVHD reactions.[80,81] In adults, lactase is mainly produced by microorganisms, including *Actinobacteria*, *Proteobacteria*, and *Firmicutes*.[82] In allo-HSCT patients, a high incidence of *Enterococcal* expansion, which is dependent on the disaccharide lactose, was observed. Dietary lactose deprivation inhibits the outgrowth of *Enterococcus* and decreases the severity of GVHD.[83] Additionally, the damage caused by GVHD to the intestine may also contribute to the proliferation of *Enterococcus* in the intestinal environment, suggesting that a lactose-free diet may be a new treatment strategy.[84]

In terms of GVHD prevention, previous studies have detected the microbial communities and predicted the risk of GVHD by analyzing post-transplantation samples.[85,86] Zargari Marandi et al[87] investigated the association between the abundance of gut bacteria in pre-transplantation fecal samples and the occurrence of GVHD, which indicates that the gut microbiota can serve as a predictive biomarker for GVHD risk.

5.4. Novel treatments

The changes in gut microbiota and metabolites provide new strategies for disease treatment. FMT is increasingly viewed as an effective method for restoring gut microbiota diversity. Some studies have shown that FMT has a positive effect on alleviating post-transplant GVHD in patients.[72,74,80] However, FMT has also shown certain risks in some clinical trials, and its safety needs further verification.[88] Recent data showed that the transplantation mortality rate associated with FMT is 0.02%, and autologous FMT (auto-FMT) may be safer than allogeneic FMT.[89] In addition to FMT, nutritional regulation has also been investigated. Compared to parenteral nutrition, intestinal nutrition supplementation for post-transplant patients promotes the restoration of gut microbiota diversity and increases the abundance of SCFA-producing bacteria.[90] Supplementation of probiotics also has certain positive effects, but more clinical trials are needed to verify considering the uncertain safety.[72,74,88,90]

6. CONCLUSIONS

Increasing evidence presented the role of gut microbiota in the context of normal hematopoiesis and hematologic disease. The depletion of gut microbiota resulted in the hematopoietic defect, suggesting the crucial role in hematopoietic steady-state. During the process of hematopoiesis, gut microbiota got

involved in controlling the self-renewal and differentiation of HSCs through several mechanisms, such as SCFA, LPS, and bacterial DNA. Therefore, there is a close connection between gut microbiota and the hematological system. This suggests that those related metabolites, bacterial products, and bacterial taxa can be used as supplementary therapies to benefit patients.

Aged HSCs are accompanied by impaired hematopoietic reconstitution and elevated risks of hematopoietic malignancies. Therefore, rejuvenating the aged HSCs will be beneficial to organism status. However, novel strategies need to be developed for improving aged HSC. Increased intestinal permeability promoted the leakage of microbial products into blood, then activated the response of inflammation further, including IL-1 expression. However, the knockout of IL-1 receptor decreased the expression of inflammatory genes in HSCs, suggesting the targeting gut microbiota has the potential to rejuvenate the aged HSCs. In addition, improving the gut barrier helps prevent the inflammatory activation and is another strategy mitigate HSCs aging. Fortunately, it had been demonstrated that FMT from young mice to aged mice and the supplement of specific SCFA to aged mice were beneficial for the restoration of hematopoiesis in aged mice.

In hematological diseases, the researchers also investigated the potential function of gut microbiota as a biomarker for disease diagnosis and developed algorithm models for personalized risk assessment. Many studies have demonstrated the crucial role gut microbiota plays in the occurrence and progression of GVHD. It is expected that more methods of targeted treatment can be found through the analysis of specific microbial communities. The therapeutic effect may probably be improved via the utilization of FMT, probiotic or metabolite supplementation, and dietary regulation.

All in all, more and more evidence show that gut microbiota can not only affect the occurrence and development of hematological diseases, but also provide new directions for disease diagnosis, treatment, and prevention of complications. However, the research on gut microbiota is challenging as most of the samples come from patients undergoing chemotherapy, immunotherapy, or antibiotic treatment, which can also affect the gut microbiota. The specific mechanisms, by which gut microbiota regulates the hematological system, still require further exploration, and more large-scale clinical trials are needed to validate its application during therapy. Big data analysis is becoming a powerful tool in research, and it will be helpful to reveal the bidirectional relationship between microbiota and diseases in the future.

AUTHOR CONTRIBUTIONS

Y.L., B.Z., and L.J. drafted the original manuscript; P.Q., H.C., and T.C. reviewed and edited the manuscript.

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