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Review

Gut Microbiota in Hematologic Malignancies: Current Status and Innovative Framework Development

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Abstract

Patients with hematologic malignancies often suffer from gut microbiota dysbiosis after chemotherapy, radiotherapy, or hematopoietic stem cell transplantation, which leads to severe complications such as mucositis, graft-versus-host disease (GVHD), multidrug-resistant bacterial infections, and persistent immune dysfunction. These adverse events greatly compromise treatment tolerance, long-term survival, and patients' quality of life. Microecological interventions, including fecal microbiota transplantation (FMT) and probiotic therapies, have exhibited great potential for preventing and managing treatment-related complications and enhancing anti-tumor effects. Nevertheless, a standardized research system has not yet been established in this field, and multiple technical bottlenecks remain unresolved. This article elaborates on five major challenges: limitations in microbiota detection and prognostic modeling, inadequate intervention strategies for gastrointestinal complications, translational obstacles of FMT in GVHD treatment, difficulties in the microecological control of multidrug-resistant infections, and unclear synergistic mechanisms between gut microbiota and immunotherapy. An innovative research framework covering spatiotemporal multi-omics analysis, AI-driven predictive modeling, stratified precision intervention, and mechanistic exploration is accordingly proposed. This framework helps interpret the regulatory rules of the microbiota-immune-metabolic axis, promotes the standardization and individualization of microecological therapies, and facilitates the advancement of precision medicine for hematologic malignancies.

Key words: Gut microbiota; hematologic malignancies; fecal microbiota transplantation; graft-versus-host disease; precision intervention.

1. Introduction

Hematologic malignancy patients undergoing chemotherapy, radiotherapy, or hematopoietic stem cell transplantation are highly susceptible to gut microbiota dysbiosis, which subsequently induces a series of severe complications, including mucositis, graft-versus-host disease (GVHD), multidrug-resistant (MDR) bacterial infections, and persistent immune dysfunction. These complications significantly impair treatment tolerance and reduce long-term survival and quality of life (1).In recent years, microecological interventions such as fecal microbiota transplantation (FMT) and probiotic-based therapies have demonstrated substantial potential in preventing and managing treatment-

related complications in hematologic malignancies. Accumulating evidence indicates that the gut microbiota can regulate host immune responses, mediate metabolic secretion, and restore intestinal mucosal barrier integrity, thereby alleviating treatment-related toxicity and synergistically enhancing antitumor efficacy. However, microecological research in hematologic malignancies has not yet established a systematic framework. Three major technical bottlenecks remain: (1) the lack of a comprehensive dynamic microbiota monitoring system, limiting real-time characterization of microbiota–host interactions throughout treatment; (2) the absence of individualized intervention strategies, with FMT lacking standardized and stratified clinical application protocols; and (3) fragmented understanding of microbiota–immune–metabolic regulatory mechanisms, with key regulatory networks yet to be elucidated, significantly hindering the development and clinical translation of precision interventions. Schematic overview of research status and construction of innovation system of gut microecology in hematological malignancies in Figure 1.

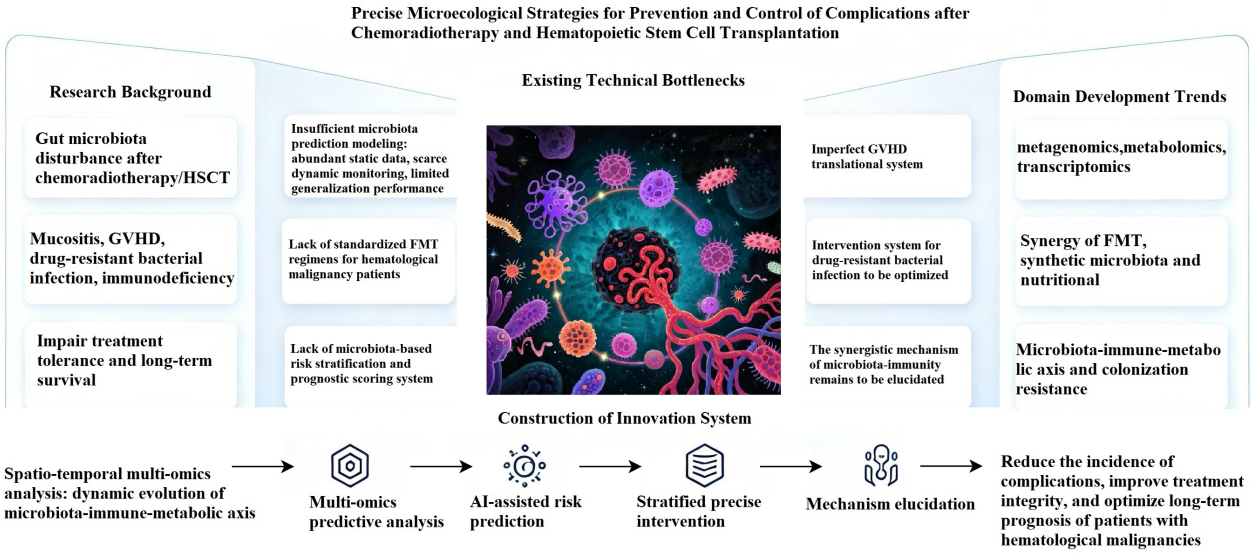


Figure 1. Gut microecology in hematological malignancies: research status and innovative framework

2. Key Technical Bottlenecks in the Field

Based on current advances in hematologic malignancy management and gut microbiome research, major challenges are concentrated in five domains: microbiota-based predictive modeling, gastrointestinal complication management, GVHD clinical translation, MDR infection control, and microbiota–immune interaction mechanisms.

2.1 Limitations in Microbiota Detection and Prognostic Modeling

High-throughput sequencing technologies, including 16S ribosomal RNA (16S rRNA) sequencing and metagenomic sequencing, have been widely used to characterize gut microbiota in hematologic malignancies. Studies have demonstrated a significant negative correlation between gut microbiota diversity after chemotherapy and mucositis severity. A reduction in the abundance of Faecalibacterium prausnitzii, an anti-inflammatory bacterium, has been associated with a markedly increased risk of oral mucositis. However, most existing studies rely on single time-point cross-sectional analyses, lacking continuous longitudinal microbiota data across the treatment course. This limitation prevents capturing temporal dynamics of microbiota alterations, resulting in poor generalizability and limited predictive performance of current microbiota-based prognostic models, which are insufficient for clinical early-warning applications (2).

2.2 Limitations of Microecological Interventions for Gastrointestinal Complications

Inflammatory bowel disease is a common and severe gastrointestinal complication following chemotherapy and transplantation in hematologic malignancies. Randomized controlled trials have confirmed that FMT can significantly improve clinical remission rates in inflammatory bowel disease patients (3). However, existing evidence is

primarily derived from the general population, with limited data in immunocompromised hematologic malignancy patients. Furthermore, the synergistic effects of FMT combined with adjunctive therapies, such as peptide-based nutritional support and enteral nutrition modulation, as well as optimal intervention timing and efficacy enhancement mechanisms, remain unclear. Consequently, standardized intervention protocols tailored to hematologic malignancies are lacking.

2.3 Barriers to Clinical Translation of FMT for GVHD Prevention and Treatment

Following allogeneic hematopoietic stem cell transplantation, the incidence of GVHD ranges from 30% to 50% (4). Several international guidelines have recommended FMT as a second-line therapy for steroid-refractory GVHD (5,6). Mechanistically, FMT reshapes the intestinal Clostridiales community and modulates bile acid metabolism, thereby suppressing T helper 17-mediated inflammatory responses and reducing interleukin-17 levels by approximately 40%. Despite these advances, significant translational gaps remain. In particular, microbiota-based GVHD risk stratification and prognostic scoring systems have not been established, limiting patient stratification and hindering the standardized and individualized clinical application of FMT.

2.4 Challenges in Microecological Strategies for MDR Infection Control

Patients with hematologic malignancies are highly susceptible to MDR infections due to prolonged immunosuppression and extensive use of broad-spectrum antibiotics, with infection rates reaching up to 40% (7). FMT can restore gut microbial homeostasis and colonization resistance, competitively inhibiting MDR pathogen colonization and proliferation, achieving clearance rates of carbapenem-resistant Enterobacteriaceae of up to 90% (8). However, these patients typically exhibit low microbiota diversity, depletion of beneficial bacteria, and high pathogen burden, which directly affect FMT engraftment efficiency and therapeutic outcomes. Currently, there is a lack of optimized donor selection criteria, microbial composition strategies, and intervention frequency protocols tailored to this population.

2.5 Research Bottlenecks in the Synergistic Mechanism of Microbiota and Immunotherapy

Specific gut microbial species exhibit significant immunomodulatory effects. For example, Akkermansia muciniphila can activate the Toll-like receptor 4/interferon-γ signaling pathway, enhancing the efficacy of programmed cell death protein 1 (PD-1) inhibitors and increasing overall response rates by up to 2.5-fold (9). This highlights microbiota modulation as a promising strategy to overcome immunotherapy resistance in hematologic malignancies. However, key gaps remain, including safety risks of combined microbiota–immune checkpoint inhibitor (ICI) therapy, mechanisms underlying immune-related colitis, dose–response relationships, and individualized patient selection criteria. These limitations hinder the standardization and clinical implementation of combination therapies.

3. Current Research Status

Gut microbiota profiling has become an important approach for predicting complications, evaluating therapeutic efficacy, and assessing prognosis in hematologic malignancies. Current mainstream technologies include 16S rRNA sequencing and metagenomic sequencing, enabling detailed characterization of microbiota structure throughout treatment. Clinical studies have shown that chemotherapy and radiotherapy significantly reduce microbiota diversity, typically reflected by a ≥30% decrease in the Shannon index. A reduced abundance of Faecalibacterium prausnitzii is associated with an increased risk of mucositis. A domestic study reported that when the relative abundance of Bacteroidetes falls below 15%, the risk of severe mucositis increases by 3.8-fold. Nevertheless, most studies remain limited to single time-point sampling, and insufficient dynamic monitoring restricts predictive accuracy (10). Future research trends focus on integrating multi-omics data and machine learning approaches, such as Extreme Gradient Boosting (XGBoost) algorithms, to improve predictive performance and elucidate underlying mechanisms through functional gene annotation.

In the transplantation setting, allo-HSCT remains a curative treatment for hematologic malignancies but is associated with high rates of complications, including microbiota dysbiosis, MDR infections, and GVHD. The gut microbiome serves as a major reservoir of antimicrobial resistance genes, and a stable microbiota confers colonization resistance, preventing pathogen invasion and maintaining immune barrier integrity.However, conditioning regimens, extensive antibiotic exposure, and post-transplant immunodeficiency disrupt microbiota composition,

leading to loss of colonization resistance and increased susceptibility to infections and inflammatory complications.Large cohort studies have demonstrated that higher gut microbiota diversity is associated with reduced infection rates and improved long-term outcomes in acute myeloid leukemia patients (11). Conversely, broad-spectrum antibiotics suppress beneficial bacteria, such as Clostridium species, and increase transplant-related mortality (12).

Quantitative associations between microbiota composition and transplant outcomes have been validated. Enrichment of beneficial taxa, including Lachnospiraceae and Ruminococcaceae, is associated with reduced transplant-related mortality, whereas overgrowth of pathogenic taxa such as Enterobacteriaceae and Enterococcus is linked to poor immunotherapy response, increased GVHD incidence, and higher mortality and bloodstream infection rates (13,14). Additionally, dominance of γ-Proteobacteria post-transplant is an independent predictor of pulmonary infections. FMT can restore microbial homeostasis, eliminate high-risk pathogens, and re-establish colonization resistance, providing a novel strategy for complication prevention. Multiple meta-analyses have confirmed that low microbiota diversity is an independent risk factor for reduced overall survival and increased transplant-related mortality (15), and is negatively associated with GVHD incidence and long-term survival (16). Using the inverse Simpson index, one study demonstrated that patients with low, intermediate, and high microbiota diversity had 3-year overall survival rates of 36%, 60%, and 67%, respectively, and transplant-related mortality rates of 53%, 23%, and 9% (P = 0.019 and 0.003), highlighting the critical role of microbiota homeostasis.

In the field of immunotherapy, ICIs have been widely applied in lymphoma and other hematologic malignancies, significantly improving clinical outcomes (17). ICIs primarily target PD-1, programmed death-ligand 1, and cytotoxic T-lymphocyte-associated protein 4, restoring antitumor immune responses by blocking inhibitory signaling pathways. However, response rates remain limited (20%–40%), with substantial inter-individual variability and resistance. The gut microbiota has emerged as a key regulator of the tumor immune microenvironment and T-cell function, representing a novel avenue for overcoming immunotherapy resistance (18).

4. Future Development Trends

Current research on the gut microbiota in hematologic malignancies is limited by a predominance of static analyses, a lack of longitudinal dynamic data, and suboptimal predictive model performance, which collectively fail to meet the demands of precision medicine. Future advancements in this field will be driven by the integration of multi-omics approaches and artificial intelligence (AI)-based modeling, thereby overcoming the limitations of conventional study designs. By integrating metagenomics, metabolomics, and transcriptomics data, it will be possible to longitudinally track dynamic alterations in microbial composition, functional genes, and metabolite profiles throughout chemotherapy, radiotherapy, and transplantation. Furthermore, machine learning algorithms such as XGBoost can be leveraged to iteratively optimize predictive models, significantly improving early warning accuracy for complications including mucositis, GVHD, and MDR infections. Combined with functional gene annotation, these approachess will enable in-depth characterization of microbiota–host interaction mechanisms, thereby addressing current gaps in mechanistic understanding.

In the context of hematopoietic stem cell transplantation, existing studies have primarily established correlations between individual microbial taxa and clinical outcomes, but lack integrated and standardized microbiota-based prognostic systems. Future research should focus on two major directions: the development of microbiota–immune integrated prognostic models and the advancement of next-generation microecological therapeutics. Specifically, single-cell sequencing technologies can be employed to elucidate key pathways through which the gut microbiota regulates T-cell exhaustion and immune dysregulation, thereby clarifying the molecular mechanisms by which the microbiota–immune axis mediates transplant-related complications. In parallel, integrating microbial biomarkers, immune parameters, and baseline clinical characteristics will enable the construction of high-precision composite prognostic scoring systems for patient stratification and individualized management. Moreover, limitations associated with conventional FMT—including donor dependency, variable efficacy, and limited safety controllability—should be addressed through the development of standardized synthetic microbial consortia, enabling precise and targeted reconstruction of the gut microbiota following transplantation.

In the field of immunotherapy, given the limited response rates and unclear mechanisms of resistance to ICIs, future efforts should prioritize the development of synergistic therapeutic strategies combining microbiota-targeted interventions with ICIs. This includes systematic identification of key beneficial microbial species capable of enhancing ICI efficacy, as well as mechanistic elucidation of how the microbiota reverses immune resistance and promotes antitumor immunity. In addition, rigorous evaluation of the safety profile of combination therapies is required, with particular emphasis on elucidating the mechanisms underlying immune-related colitis and defining dose–response relationships. Optimization of these combined therapeutic strategies will provide a novel translational pathway to improve immunotherapy outcomes in hematologic malignancies.

5. Establishing an Innovative Research Framework for Microecological Applications in Hematologic Malignancies

Given the aforementioned limitations in gut microbiota research in hematologic malignancies—including inadequate dynamic monitoring systems, lack of individualized intervention strategies, and fragmented mechanistic insights—it is imperative to establish a systematic, multidimensional, and clinically translatable research framework. Such a framework should aim to overcome current technical bottlenecks while bridging gaps between fundamental research and clinical application. This proposed innovation system is structured around four core dimensions: spatiotemporal multi-omics analysis, intelligent predictive modeling, stratified precision intervention, and mechanistic elucidation, as outlined below.

5.1 Integration of Multi-Omics Technologies to Decipher Spatiotemporal Dynamics of the Microbiota–Immune–Metabolic Axis

By integrating 16S rRNA sequencing, untargeted/targeted metabolomics, and single-cell transcriptomics, a comprehensive multi-omics analytical framework can be established to dynamically monitor gut microbiota composition, immune cell subset remodeling in intestinal and peripheral compartments, and systemic metabolic fluctuations throughout chemotherapy and transplantation.Particular emphasis should be placed on elucidating the temporal and spatial regulatory patterns by which key microbial taxa mediate immune dysregulation and metabolic reprogramming under treatment-induced stress. This approach will enable precise identification of microbial biomarkers, differential metabolites, and immune targets associated with mucosal injury, inflammatory activation, and immunosuppression. Ultimately, it will provide a systematic understanding of how coordinated disruption of the microbiota–immune–metabolic axis drives treatment-related complications, thereby overcoming the limitations of conventional static and single-omics studies.

5.2 AI-Driven Development of High-Precision Clinical Risk Prediction Models

Leveraging large-scale clinical cohorts incorporating microbiota profiles, baseline clinical characteristics, and outcome data, machine learning approaches such as XGBoost can be applied to develop robust predictive models for complications, including GVHD and multidrug-resistant infections. Through rigorous training, validation, and testing workflows, model parameters can be continuously optimized to improve predictive accuracy and specificity for post-transplant complications, including acute and chronic GVHD, microbial colonization, and invasive infections. This strategy addresses the limitations of traditional single-parameter prediction models and provides a foundation for intelligent risk stratification and early clinical intervention.

5.3 Stratified and Individualized Precision Intervention Based on Microbiota Profiling

To overcome the limitations of current uniform intervention strategies, patients should be stratified based on microbiota diversity, pathogen burden, abundance of protective taxa, and functional characteristics. For distinct subgroups—such as those at high risk of GVHD, high multidrug-resistant pathogen burden, or severe dysbiosis—tailored intervention strategies should be developed, including optimized FMT protocols, donor selection criteria, and adjunctive nutritional support. This approach enables the establishment of a standardized clinical workflow integrating microbiota profiling, risk stratification, and precision intervention, thereby addressing current challenges related to limited efficacy, poor reproducibility, and lack of personalization in microecological therapies.

5.4 Mechanistic Elucidation of Microbiota Remodeling Induced by Fecal Microbiota Transplantation

Focusing on the prevention and management of treatment-related complications, mechanistic studies

should investigate key processes, including restoration of colonization resistance, bile acid metabolism reprogramming, regulation of T-cell–mediated inflammatory pathways, and re-establishment of immune homeostasis. A systematic dissection of the molecular mechanisms by which FMT restores microbial balance, suppresses excessive inflammation, reverses immune dysfunction, and eliminates resistant pathogens is essential. Identifying therapeutic targets, effector microbial taxa, and key metabolic pathways will address current knowledge gaps and provide a theoretical foundation for the standardization and clinical translation of microecological interventions. Building upon these four pillars, a novel paradigm of multidimensional regulation along the microbiota–immune–metabolic axis can be established in hematologic malignancies. This framework will enable the independent development of high-precision microbiota-based predictive models and individualized intervention strategies tailored to this patient population, ultimately advancing precision medicine in clinical practice. From a clinical perspective, precision microecological interventions have the potential to reduce the incidence of post-transplant complications, including GVHD and multidrug-resistant infections, minimize treatment interruptions caused by severe mucosal injury, and significantly improve treatment continuity and safety.Although substantial progress has been made in applying gut microbiota-based strategies to complication prevention and prognosis improvement, major challenges remain, including insufficient longitudinal monitoring, lack of individualized interventions, and incomplete mechanistic understanding.Future research should therefore focus on three key directions: deep multi-omics integration, AI-driven predictive modeling, and the development of standardized precision intervention systems. Establishing such a comprehensive innovation framework will not only overcome current technical limitations but also refine the theoretical basis of microbiota-mediated regulation of treatment-related complications. Ultimately, this will provide robust scientific and translational support for optimizing clinical management, improving long-term outcomes, and enhancing quality of life, while promoting the large-scale and standardized application of microecological technologies in precision treatment of hematologic malignancies.

Declarations

1. ***Consent to publication***
   We declare that all authors agreed to publish the manuscript in this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2. ***Ethical approval and consent of participants***
   None.
3. ***Disclosure of conflict of interests***
   We declare that no conflict of interest exists in this work.
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5. ***Availability of data and material***
   We declare that the data supporting the results reported in the article are available in the published article and from the corresponding author upon reasonable request.
6. ***Authors' Contributions***
   The author was solely responsible for conceptualization, literature retrieval, data sorting, manuscript drafting, revision, and final approval of this review.
7. **Acknowledgement**
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8. ***Authors' biography***
   None.

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