REVIEW ARTICLE

Microbial Influences on Leukaemia: A New Frontier in Haematological Research

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ABSTRACT

Leukaemia, a complex group of haematological malignancies, is influenced not only by genetic mutations and the bone marrow microenvironment but also by the human microbiota. Emerging evidence shows that the microbiome contributes to leukaemia pathogenesis, progression, and treatment outcomes through its effects on haematopoiesis, immune regulation, and microbial metabolite production. This review aims to explore how microbial metabolites regulate haematopoietic stem cells and immune function; assess how dysbiosis contributes to leukemogenesis and therapy resistance; evaluate the therapeutic potential of probiotics, prebiotics, and faecal microbiota transplantation (FMT); and identify challenges and future directions for microbiome-informed, personalised leukaemia care. Microbial dysbiosis is associated with chronic inflammation, impaired immune surveillance, and altered leukemic cell behaviour. Additionally, microbiota composition affects treatment efficacy and toxicity by modulating drug metabolism, mucosal integrity, and immune responses. Interventions such as probiotics, prebiotics, and FMT demonstrate potential in restoring microbial balance and improving treatment outcomes. The microbiota represents a potential yet underexplored dimension of leukaemia research and care. Further studies, particularly large-scale clinical trials, are required to validate microbiota-targeted strategies and facilitate their integration into clinical practice to enhance therapeutic efficacy and patient outcomes.
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INTRODUCTION

Leukaemia, a complex and heterogeneous group of haematological malignancies, arises from genetic and epigenetic alterations that disrupt normal haematopoiesis and lead to uncontrolled proliferation of leukemic cells. Traditionally, leukaemia research has focused on chromosomal abnormalities, gene mutations, and bone marrow microenvironmental factors as key contributors to disease initiation and progression (1, 2). While these intrinsic factors remain central to leukaemia biology, growing evidence highlights the significance of extrinsic factors, particularly the human microbiota, in modulating leukaemia pathophysiology and treatment responses (3, 4).

The microbiota is a diverse and dynamic ecosystem of microorganisms, including bacteria, fungi, viruses, and archaea, that inhabit various body sites, with the gut microbiota being the most extensively studied. It is estimated that the human gut harbours approximately 10^14 microbial cells, outnumbering human cells, and encodes over 3 million genes, greatly expanding metabolic and immunological capabilities (5). These microorganisms play a critical role in maintaining host homeostasis by regulating immune development, inflammation, and metabolic processes (6).

Recent studies underscore the importance of microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan derivatives, in shaping immune responses and influencing haematopoiesis. SCFAs, including acetate, butyrate, and propionate, act through G-protein-coupled receptors (GPCRs) to modulate T-cell differentiation and cytokine production, ultimately influencing bone marrow function and leukemogenesis (7, 8). Dysbiosis, characterized by an imbalance in microbial composition, has been implicated in hematopoietic abnormalities and leukemic transformation due to increased inflammation and oxidative stress (9).

Moreover, the microbiota interacts bidirectionally with leukaemia therapies. For example, gut bacteria can metabolize chemotherapeutic drugs, altering their efficacy and toxicity (10). Antibiotic-induced disruption of the gut microbiota has been shown to impair responses to immune checkpoint inhibitors and hematopoietic stem cell transplantation (HCT), highlighting the microbiota's role in modulating antitumor immunity (4, 11). Given these insights, microbiota-targeted interventions, including probiotics, prebiotics, and FMT, have emerged as potential strategies to improve treatment outcomes and mitigate therapy-related complications.

Despite these advances, the precise mechanisms linking microbial dysbiosis to leukemogenesis remain poorly defined, and the role of specific microbial taxa and metabolites in modulating therapy responses is not well understood. Most studies to date have focused on solid tumours or general cancer models, leaving a significant knowledge gap in haematological malignancies. Furthermore, the lack of large-scale clinical trials and mechanistic clarity limits the integration of microbiota-based strategies into routine leukaemia care (12).

Given these challenges, microbiota-targeted interventions, including probiotics, prebiotics, and FMT, have emerged as potential strategies to improve treatment outcomes and mitigate therapy-related complications. However, significant barriers such as inter-individual variability in microbiome composition and regulatory hurdles must be addressed before translation into clinical practice is feasible (13, 14).

To address these gaps, this narrative review synthesizes the current evidence on the role of the microbiota in leukaemia. The review discusses mechanistic insights into microbiota–leukaemia interactions, including how microbial metabolites regulate haematopoietic stem cells and immune function. It further examines the impact of dysbiosis on leukemogenesis and treatment resistance, highlighting how microbial imbalances shape disease progression and therapeutic responses. In addition, the review evaluates the therapeutic potential of microbiota-based interventions such as probiotics, prebiotics, and FMT, while outlining key challenges that currently limit their clinical translation. Finally, the review identifies knowledge gaps and proposes future directions to guide the integration of microbiome science into leukaemia management, with the ultimate goal of advancing personalised approaches and improving patient outcomes.

MICROBIOTA AND HAEMATOPOIESIS

Normal Haematopoiesis and the Microbiota

Haematopoiesis, the process of blood cell formation, occurs in the bone marrow and involves the differentiation of HSCs into various blood and immune cells. Recent evidence suggests that the gut microbiota plays a vital role in regulating haematopoiesis through microbial-derived metabolites and immune modulation (15). Key mechanisms involve SCFAs such as butyrate and propionate, which are produced by commensal bacteria, including Firmicutes and Bacteroidetes. These SCFAs act on bone marrow stromal cells via G-protein-coupled receptors such as GPR43 to regulate HSC proliferation and differentiation (8). SCFAs also promote the production of anti-inflammatory cytokines, such as IL-10, that support HSC maintenance and quiescence (7).

Experimental evidence from germ-free mouse models provides compelling support for these findings. Germ-free mice exhibit reduced levels of SCFAs, which correlate with impaired myeloid and erythroid cell production(16, 17, 18). Notably, reintroducing SCFA-producing bacteria or supplementing SCFAs restores haematopoiesis, highlighting the microbiota's role as a critical modulator of hematopoietic balance (19). The microbiota also influences systemic inflammation, which impacts haematopoiesis. For instance, gut dysbiosis induced by antibiotics or dietary changes can trigger systemic inflammation, altering cytokine profiles and skewing HSC differentiation toward myelopoiesis (20). These findings suggest that maintaining microbiota homeostasis is essential for preserving hematopoietic integrity.

Microbiota-Induced Leukemogenesis

Leukemogenesis, the process by which normal hematopoietic cells transform into malignant leukaemia cells, is influenced by multiple factors, including chronic inflammation and oxidative stress driven by microbial dysbiosis (21).

Microbial dysbiosis has been shown to induce low-grade chronic inflammation, which plays a significant role in leukemogenesis. Dysbiosis elevates pro-inflammatory cytokines such as interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha (TNF-α), both of which promote HSC exhaustion and DNA damage, increasing the likelihood of leukemic transformation (22). Studies have demonstrated that patients with leukaemia often exhibit altered gut microbiota compositions characterized by a reduction in beneficial bacteria such as Lactobacillus and Bifidobacterium, and an increase in pro-inflammatory species such as Enterobacteriaceae and Escherichia coli. (11). In murine models, antibiotic-induced gut microbiota depletion has been associated with impaired immune surveillance, allowing for the unchecked proliferation of pre-leukemic clones (19). Additionally, gut microbiota-derived lipopolysaccharides (LPS) have been implicated in activating Toll-like receptor 4 (TLR4) signalling, leading to myeloid expansion and enhanced leukemogenicity potential (13).

Another mechanism by which microbiota influences leukemogenesis is through oxidative stress. Gut dysbiosis

has been linked to increased levels of reactive oxygen species (ROS) in bone marrow progenitors, a hallmark of pre-leukemic conditions (10). In antibiotic-treated mouse models, ROS accumulation in HSCs has been correlated with mitochondrial dysfunction and impaired DNA repair mechanisms, leading to genomic instability and the emergence of leukemic clones (20). In human studies, patients with acute myeloid leukaemia (AML) and chronic lymphocytic leukaemia (CLL) have shown increased oxidative stress markers in both peripheral blood and bone marrow samples, which correlate with alterations in gut microbiota composition(23). Certain pathogenic bacteria, including Helicobacter hepaticus and Bacteroides fragilis, have been shown to produce genotoxins that exacerbate ROS generation and promote leukemic transformation (22).

Given these findings, targeting the microbiota to reduce inflammation and oxidative stress represents a promising avenue for leukaemia prevention and treatment. Strategies such as probiotic supplementation, dietary modifications, and FMT are being explored to restore microbial balance and mitigate leukemic progression (14).

MICROBIOTA-IMMUNE SYSTEM INTERACTIONS IN LEUKAEMIA

Shaping Immune Responses

The gut microbiota plays a crucial role in shaping systemic immune responses, including T-cell differentiation and activation. Certain bacterial species, such as Clostridia, have been shown to enhance regulatory T cell (Treg) differentiation via microbial metabolites like butyrate, which helps modulate inflammatory responses in conditions such as acute lymphoblastic leukaemia (ALL) (24, 25). A landmark study by Schluter et al. (2020) demonstrated that patients with AML exhibit significantly reduced gut microbial diversity, which was associated with impaired T-cell activation and increased infection susceptibility following chemotherapy. Importantly, this study used longitudinal microbiome and immune profiling, revealing that microbiota depletion not only disrupts microbial ecology but also alters the systemic immune landscape, leading to an exaggerated state of treatment-related immunosuppression. This finding is particularly significant because it provides direct clinical evidence linking microbiota composition to immune dysfunction in leukaemia patients, suggesting that microbial loss during chemotherapy is not merely a side effect but a driver of poor immune recovery and infectious complications (26).

The gut microbiota plays a vital role in shaping host antitumor immune responses, influencing both innate and adaptive immunity. One area where this interaction is particularly evident is in the context of immune checkpoint inhibitors (ICIs), a class of immunotherapies that target inhibitory pathways such as programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). These checkpoints normally function to maintain self-tolerance and prevent autoimmunity, but in cancer, they are exploited by malignant cells to evade immune detection. By blocking these pathways, ICIs restore T-cell effector functions and enhance cytotoxic activity against tumour cells (27).

Recent research has highlighted the critical role of the gut microbiota in determining ICI efficacy. Certain bacterial taxa, particularly Bifidobacterium spp. and Akkermansia muciniphila, have been associated with enhanced ICI responses in solid tumours, including melanoma and lung cancer. Routy et al. (2018) demonstrated that the presence of these bacteria correlated with improved immune surveillance, greater intertumoral CD8+ T-cell infiltration, and enhanced systemic T-cell activation. Conversely, dysbiosis or broad-spectrum antibiotic use was associated with poor ICI efficacy, suggesting that microbial composition can act as a determinant of therapeutic response (28).

Although most evidence comes from solid tumours, emerging studies suggest potential parallels in haematological malignancies, including leukaemia. Since leukaemia progression is strongly influenced by immune evasion and dysfunction of T-cell responses, microbiota-driven modulation of immune checkpoints may similarly shape treatment outcomes. Early preclinical models indicate that restoring microbial diversity may enhance the effectiveness of ICIs by reducing T-cell exhaustion and promoting antitumor immunity in leukaemia contexts (29). Thus, while direct clinical data in leukaemia are limited, the microbiome–ICI axis represents a promising avenue for therapeutic optimization.

One area where microbiota influence is becoming increasingly evident is in chimeric antigen receptor (CAR) T-cell therapy for hematologic malignancies. The composition and diversity of the gut microbiome have been found to impact CAR T-cell efficacy and toxicity. A study by Peled et al. (2020) revealed that leukaemia patients with greater microbial diversity prior to CAR T-cell infusion experienced improved treatment responses and a lower incidence of severe cytokine release syndrome (CRS). This finding highlights the potential of microbiome modulation as a strategy to optimize CAR T-cell therapy outcomes (11). Table I presents key studies that link gut microbiota composition to immune responses in leukaemia and its associated therapeutic interventions.

Inflammation as a Catalyst for Leukaemia

Chronic inflammation is a well-recognized driver of leukemogenesis, with the gut microbiota playing a crucial role in modulating inflammatory responses. Microbial dysbiosis can lead to persistent immune activation,

Table I: Key studies linking the gut microbiota to immune responses in leukaemia and related therapies

Author/Year	Study Model/ Population	Microbiota Finding	Immune Effect	Clinical/Therapeutic Implication
Arpaia et al., 2013; Atarashi et al., 2013 (25, 30)	Mouse models	SCFAs (butyrate/propionate) and Clostridia consortia promote Treg differentiation	Enhances immune tolerance, reduces inflammation	Potential use of SCFA-producing bacteria to regulate immune balance in leukaemia settings (e.g., ALL)
Schluter et al., 2020 (26)	Cancer patients receiving allo-HCT (longitudinal)	Specific gut taxa associated with higher lymphocyte/neutrophil counts; FMT enhances recovery	Modulates immune cell reconstitution dynamics	Establishes a quantitative link between gut microbiota and immune recovery; supports microbiota preservation during HCT
Routy et al., 2018 (28)	Cancer patients (solid tumours) undergoing ICI therapy	Enrichment of *Akkermansia muciniphila, Bifidobacterium* correlates with better responses	Enhances T-cell activation and immune surveillance	Suggests microbiota composition could influence immunotherapy success in leukaemia
Peled et al., 2020 (11)	Allogeneic HCT recipients (hematologic malignancies)	Low microbial diversity at engraftment predicts higher mortality	Impaired immune recovery linked to high mortality	Microbiome diversity as a prognostic biomarker; urgency for microbiota-preserving strategies
Eriguchi et al., 2012 (31)	Mouse model of GVHD following allo-HCT	GVHD damages Paneth cells, reducing α-defensin and inducing dysbiosis	Worsens intestinal inflammation and GVHD severity	Highlights the microbiota's role in GVHD pathogenesis and need to maintain microbial ecology haematological cancers

resulting in hematopoietic stem and progenitor cell (HSPC) exhaustion, increased mutational burden, and ultimately, leukaemia initiation. Disruptions in the gut microbial community contribute to an inflammatory microenvironment that supports leukemic progression (9).

One key mechanism linking microbial dysbiosis to leukaemia involves the overgrowth of pathogenic bacteria, particularly Enterobacteriaceae and Escherichia coli, which can chronically activate the NF-κB signalling pathway. This activation promotes the survival and proliferation of leukemic stem cells, sustaining disease progression (32, 33). Additionally, microbial metabolites play a significant role in inflammatory signalling. LPS derived from Enterobacteriaceae activate TLR4, triggering the release of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6. These inflammatory mediators establish a pro-leukemic bone marrow microenvironment, further supporting malignant transformation (34, 35).

Clinical evidence highlights the link between microbiota-driven inflammation and leukaemia outcomes. Elevated levels of C-reactive protein (CRP), a marker of systemic inflammation, have been associated with gut microbiota imbalances in elderly leukaemia patients. Higher CRP levels correlate with poor treatment responses and increased mortality, suggesting that inflammation induced by microbial dysbiosis contributes to disease severity. Furthermore, chemotherapy-induced damage to the intestinal mucosal barrier increases gut permeability, allowing translocation of pathogenic bacteria into the bloodstream. This process exacerbates systemic inflammation and heightens the risk of sepsis, a life-threatening complication in leukaemia patients (36, 37)

THERAPEUTIC POTENTIAL OF TARGETING THE MICROBIOTA

Probiotics and Prebiotics in leukaemia therapy

The potential of probiotics and prebiotics to modulate the gut microbiota, reduce inflammation, and enhance immune responses suggests they may serve as supportive strategies in leukaemia treatment (38). Probiotics, which are live microorganisms that confer health benefits to the host, may help restore microbial balance disrupted by chemotherapy or antibiotics. Prebiotics, on the other hand, are non-digestible dietary fibres that selectively stimulate beneficial bacteria, thereby maintaining a healthy gut environment. Together, these interventions can preserve intestinal barrier integrity, reduce systemic inflammation, and potentially influence therapeutic responses in leukaemia patients (39, 40)

Several studies support the therapeutic potential of these microbiota-targeted interventions. For instance, clinical trials in cancer patients have shown that specific probiotic strains, such as Lactobacillus rhamnosus GG and Bifidobacterium longum, can reduce chemotherapy-induced diarrhoea and mucositis, common complications in leukaemia treatment (41, 42). These effects not only improve patient quality of life but may also prevent secondary infections and reduce hospitalizations. Prebiotics such as inulin and fructooligosaccharides (FOS) have been shown to enhance SCFA production, particularly butyrate, which possesses anti-inflammatory and anti-cancer properties and supports hematopoietic health(43, 44).

Moreover, preclinical studies suggest that probiotics and prebiotics can positively influence immune modulation and haematopoiesis. For example, oral administration

of probiotics has been linked to increased regulatory T-cell populations and improved myeloid differentiation in murine models of leukaemia (45). These immunomodulatory effects indicate a potential role for microbiota-targeted therapies in enhancing the efficacy of conventional treatments, including chemotherapy and immunotherapy.

Although the clinical application of probiotics and prebiotics in leukaemia therapy is still in its early stages, current evidence—largely derived from preclinical animal studies and clinical trials in general oncology populations—supports their potential as safe and effective supportive care strategies. Preclinical studies in murine models of haematological malignancies by Bindels et al. (2016) have shown that probiotic administration can improve immune regulation and hematopoietic recovery (46). In parallel, human clinical trials in cancer patients (though not leukaemia-specific) have demonstrated that probiotics such as Lactobacillus rhamnosus GG and Bifidobacterium longum can reduce chemotherapy-induced diarrhoea and mucositis, thereby improving patient quality of life (47, 48). However, leukaemia-specific human trials remain scarce, and evidence is primarily extrapolated from broader oncology cohorts. Therefore, well-designed, large-scale randomized controlled trials are urgently needed to determine optimal probiotic strains, prebiotic formulations, dosages, and treatment schedules tailored to the unique microbiome profiles of leukaemia patients. Integrating these microbiota-based approaches into leukaemia care, once validated, may reduce treatment-related toxicities, enhance immune recovery, and ultimately improve clinical outcomes (38).

Faecal Microbiota Transplantation (FMT)

FMT, the process of transferring faecal material from a healthy donor into the gastrointestinal tract of a patient, has gained attention as a therapeutic approach to restore gut microbial balance in various diseases, including haematological malignancies such as leukaemia. Donor faecal material is a complex biological mixture that contains not only viable bacterial communities but also bacterial metabolites (e.g., SCFAs), bacteriophages, fungi, viruses, archaea, and extracellular vesicles, all of which may contribute to restoring host immunity and intestinal homeostasis. Standard donor stool is carefully screened for infectious agents, including multidrug-resistant organisms, to ensure safety, particularly in immunocompromised patients such as those with leukaemia. Preparations may involve fresh stool, frozen suspensions, or lyophilized capsules, with frozen or encapsulated formulations increasingly used due to better standardization and reduced risk of contamination (49). In leukaemia patients, intensive chemotherapy and antibiotic use frequently lead to gut dysbiosis, which is associated with increased inflammation, impaired immune function, and a higher risk of bloodstream infections and treatment complications. FMT has shown promise in reversing these effects by reintroducing a diverse and healthy microbial community.

Clinical studies have demonstrated the potential of FMT to improve outcomes in hematopoietic stem cell transplantation (HSCT) recipients, many of whom are leukaemia patients. For example, Taur et al. (2018) reported that FMT successfully restored microbiota diversity in patients following broad-spectrum antibiotic exposure during HSCT, potentially reducing complications such as graft-versus-host disease (GVHD) and infections (50). Moreover, a study by DeFilipp et al. (2018) showed that FMT not only re-established gut microbial diversity but also promoted immune recovery and improved T-cell function in allogeneic HSCT recipients. These outcomes imply that FMT might help with immunological reconstitution and lower systemic inflammation, two aspects that are crucial for the development of leukaemia and the effectiveness of treatment (51).

Importantly, FMT has also been used to treat recurrent Clostridioides difficile infections in immunocompromised leukaemia patients with high success rates and minimal adverse events, further supporting its safety and feasibility in this vulnerable population (52). While more large-scale clinical trials are necessary, these findings underscore the therapeutic potential of FMT as part of integrative care in leukaemia management.

Microbial Metabolites as Therapeutics

Microbial metabolites, particularly SCFAs such as butyrate, propionate, and acetate, have emerged as promising therapeutic agents in leukaemia due to their role in regulating immune responses, maintaining hematopoietic balance, and exerting anti-inflammatory and anti-cancer effects. Produced through the fermentation of dietary fibres by commensal gut bacteria, SCFAs influence various cellular processes relevant to leukaemia pathogenesis, including apoptosis, cell cycle regulation, and epigenetic modulation.

Butyrate, in particular, has garnered attention for its ability to act as a histone deacetylase (HDAC) inhibitor, thereby promoting the expression of tumour suppressor genes and inducing apoptosis in leukemic cells (53). In preclinical studies, SCFAs have been shown to enhance hematopoietic stem cell (HSC) function and reduce oxidative stress in bone marrow, contributing to a more stable and less inflammatory bone marrow microenvironment (24). Furthermore, butyrate and other SCFAs help strengthen the intestinal barrier and suppress pro-inflammatory cytokine production, potentially mitigating chemotherapy-induced mucositis and systemic inflammation common in leukaemia patients (44).

Beyond SCFAs, other microbial metabolites such as indole derivatives, bile acids, and polyamines also exhibit immunomodulatory properties and may influence leukaemia development or response to therapy. For instance, indole-3-aldehyde has been shown to activate the aryl hydrocarbon receptor (AhR) pathway, which plays a role in immune cell differentiation and gut barrier integrity (54).

While the therapeutic use of microbial metabolites in leukaemia is still largely preclinical, their multifaceted roles in immune modulation and cellular signalling make them attractive candidates for adjunctive therapies. Future clinical studies are needed to determine the efficacy, dosing, and safety of metabolite-based interventions, as well as their integration with existing leukaemia treatments.

CHALLENGES AND FUTURE DIRECTIONS

Individual Variability in the Microbiome

One of the major challenges in harnessing the microbiome for leukaemia therapy lies in the high degree of individual variability in microbial composition. Each person harbours a unique gut microbiota shaped by factors such as genetics, diet, age, environment, antibiotic exposure, and underlying disease, making it difficult to establish standardized microbiome-based interventions. This heterogeneity influences how patients respond to chemotherapy, immunotherapy, and microbiota-modulating strategies like probiotics, prebiotics, or FMT (55).

In leukaemia patients, microbial diversity and stability can vary widely, particularly after hematopoietic stem cell transplantation (HSCT) or intensive chemotherapy, leading to unpredictable outcomes. For instance, studies have shown that greater microbiota diversity is associated with improved survival and reduced complications in HSCT recipients, yet the same interventions may not yield uniform benefits across different patients (11). Additionally, individual variations in the production of microbial metabolites, such as tryptophan derivatives or short-chain fatty acids, can lead to different haematological responses and immunological regulation (3).

Another layer of complexity is the interaction between the microbiome and host genetics, which can alter immune responses and disease progression in leukaemia. Personalized approaches that consider a patient's microbiome profile, genetic background, and treatment history may be necessary to fully leverage microbiota-targeted therapies. However, the development of such precision medicine strategies is still in its infancy and requires large-scale, longitudinal studies with multi-omics integration (56).

Moving forward, future research should focus on identifying microbial signatures predictive of treatment response, developing patient-specific microbial therapeutics, and integrating microbiome assessments into routine leukaemia care. Advances in artificial intelligence and systems biology may aid in deciphering complex host-microbe interactions and translating these insights into personalized treatment protocols.

Mechanistic Insights

Despite growing evidence linking the microbiome to leukaemia progression and treatment outcomes, a major challenge remains the limited understanding of the precise mechanisms by which microbial communities influence leukemogenesis, immune modulation, and therapeutic efficacy. While correlations between microbial diversity, metabolite profiles, and treatment responses have been established, the underlying molecular pathways remain incompletely defined. This gap in mechanistic insight hinders the development of targeted microbiome-based interventions in leukaemia care (15).

Key unanswered questions include how specific microbial taxa or their metabolites directly affect hematopoietic stem cell (HSC) function, leukemic cell proliferation, and the bone marrow microenvironment. For example, although SCFAs such as butyrate have been shown to influence immune cell differentiation and epigenetic regulation (24, 53), it is still unclear how these effects translate to different leukaemia subtypes or stages. Similarly, the role of microbial-derived ligands that activate host receptors such as Toll-like receptors (TLRs) and the aryl hydrocarbon receptor (AhR) in leukemic transformation is not fully elucidated (54).

Another challenge is the complexity of host–microbiota–drug interactions. Microbes can metabolize chemotherapeutic agents, influencing their efficacy and toxicity, yet the pathways mediating these effects are not well mapped (10). Without a clear mechanistic framework, translating microbiome findings into consistent clinical benefits remains difficult.

Future studies must concentrate on integrated multi-omics techniques, which include immunophenotyping, transcriptomics, metabolomics, and metagenomics, in order to identify the causal mechanisms that connect leukaemia biology and microbial activity. In this attempt, organoid systems and animal models that replicate human hematopoietic and immunological settings can be useful tools. In the end, more mechanistic understanding will be necessary to rationally develop microbiome-based diagnostics and treatments specific to each leukaemia patient.

Clinical Implementation

There are numerous important obstacles to overcome before leukaemia patients can benefit from the use of microbiome research. The use of microbiota modulation

techniques, including as FMT, probiotics, and prebiotics, into routine leukaemia therapy is still limited, despite the growing recognition of their therapeutic potential. The absence of widely accepted criteria and regulatory frameworks for microbiome-based cancer treatments is a major obstacle that raises questions about their long-term safety, dosage, and application (57).

Moreover, clinical trials investigating microbiota-targeted interventions in hematologic malignancies are still relatively few, often limited by small sample sizes, heterogeneous patient populations, and variable methodologies. These factors make it difficult to draw definitive conclusions about efficacy and generalizability across leukaemia subtypes and treatment stages (58). Additionally, microbiome profiling technologies, such as 16S rRNA sequencing or shotgun metagenomics, are not yet routinely available in clinical settings, and standardized protocols for sample collection, processing, and interpretation are still under development (59).

Another major challenge is patient safety, particularly in immunocompromised individuals such as those undergoing chemotherapy or hematopoietic stem cell transplantation. Introducing live microbes through probiotics or FMT carries a theoretical risk of infection or unintended immune consequences, necessitating rigorous donor screening, sterility measures, and long-term follow-up (60).

In order to validate microbiome-based interventions, create safety profiles, and specify the best treatment plans, future directions should concentrate on carrying out extensive, multicentre clinical trials. Together with genetic, immunologic, and clinical data, microbiome evaluations must be incorporated into precision medicine frameworks in order to tailor treatment and enhance leukaemia patient outcomes.

CONCLUSION

The intricate relationship between the microbiota and leukaemia represents a new frontier in haematological research, influencing disease pathogenesis, immune modulation, and treatment outcomes. The microbiota regulates haematopoiesis through microbial metabolites such as SCFAs, while dysbiosis contributes to leukemogenesis via chronic inflammation and oxidative stress. Microbial composition also affects chemotherapy efficacy, immunotherapy responses, and hematopoietic recovery, with emerging interventions such as probiotics, prebiotics, FMT, and microbial-derived metabolites showing promise in improving leukaemia treatment outcomes. However, challenges such as interindividual variability, limited mechanistic insights, and regulatory concerns hinder the clinical translation of microbiota-based therapies. Future research should focus on large-scale clinical trials, multi-omics approaches, and personalized microbiome interventions to harness the full therapeutic potential of the microbiota in leukaemia care. By integrating microbiome science with haematology, microbiota-driven interventions could enhance treatment efficacy, reduce complications, and pave the way for more personalized and effective leukaemia therapies.

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