Microbial metabolomics in acute myeloid leukemia: From pathogenesis to treatment

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Abstract

Acute myeloid leukemia (AML), the most common leukemia in adults, is a biologically heterogeneous disease arising from clonally proliferating hematopoietic stem cells. Increased appreciation of novel genetic methods has improved the understanding of AML biology. Recently, the emerging field of metabolomics has indicated qualitative and quantitative alterations in metabolic profiles in AML pathogenesis, progression and treatment. Multiple metabolic and molecular pathways regulate human metabolism and host–microbiome interactions may significantly affect this biochemical machinery. Microbiota have been found to play a significant role in hematopoietic function, metabolism and immunity, contributing to AML occurrence. A large number of studies have highlighted the importance of the composition and diversity of the gut microbiota (GM) in response to treatment and prognosis in AML. Moreover, strong evidence emphasizes the detrimental link between dysbiosis and infectious complications, a leading cause of morbidity and mortality for patients with AML. Several microbiota-related mechanisms have been linked to particular changes in host physiology so far, and microbial-derived metabolites belong to one of the most important. Circulating in the body, they modulate human conditions both locally and systemically. The extensive and diverse repertoire of bacterial metabolic functions plays a critical role in numerous processes, including leukemogenesis. Integrative analysis of microbiome and metabolome data is a promising avenue for better understanding the complex relationship between the microbiota, biochemical alterations and AML pathogenesis to effectively prevent, treat and mitigate its outcomes. This review concentrates on the pathologic roles and therapeutic implications of microbe-derived metabolites in AML settings.

Key words: microbiome, gut microbiota, short-chain fatty acids, microbial metabolites, AML treatment

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Introduction

Acute myeloid leukemia (AML) is one of the most heterogeneous hematological diseases arising from clonally proliferating hematopoietic stem cells. The development of novel genetic methods has improved our understanding of AML biology. Besides genetic and epigenetic alterations, an increasing amount of data has indicated that there is a relationship between the human microbiome and the pathogenesis of AML. A large number of studies have also highlighted the potential link between the composition of the gut microbiota (GM) and response to treatment, prognosis and infectious complications, a leading cause of morbidity and mortality for patients with AML. Recently, the emerging field of metabolomics has explained multiple metabolic and molecular pathways regulating human metabolism and host–microbiome interactions that may significantly contribute to AML outcomes. Circulating in the body, microbial-derived metabolites modulate human conditions, both locally and systemically. Integrative analysis of microbiome and metabolome data is a promising avenue for better understanding the complex relationship between the microbiota, biochemical alterations and the course of AML.

In this overview, we focused on microbial metabolite-mediated interactions between the host and the microbiota and the potential mechanisms by which these metabolites exert their impacts in the context of AML. To reveal the clinical and therapeutic significance of microbial metabolomics, we reviewed previous translational research in this setting. Our findings provide a strong foundation for diagnostic and therapeutic applications of its microbiota–host interaction. Targeting specific individual microbiome-related features, including a wide variety of small compounds, emerges as the next opportunity for interventions.

Acute myeloid leukemia

Acute myeloid leukemia is a clonal disorder characterized by the presence of immature blasts and arrested differentiation of malignant myeloid blasts in the bone marrow. Recent advancements in sequencing technology and the development of analytical tools have provided a comprehensive understanding of its biology, prognosis and treatment. Leukemogenesis is broadly dependent on genetic and epigenetic alterations that lead to dysregulated gene expression and function, but there are also hematopoietic and non-hematopoietic stromal components of the leukemic microenvironment that interact with pre-leukemic and leukemic clones to promote their survival, self-renewal and resistance to therapy. Recently, an increasing amount of data has indicated various previously unknown underlying mechanisms. Among them, exploration of the human microbiota and microbial metabolites holds immense potential to further characterize AML biology. The relationship between the human microbiome and the pathogenesis of AML is not completely understood. Microbiota-induced dysregulated metabolic pathways may be implicated in leukemogenesis and the maintenance of leukemic blasts.

Identifying a whole spectrum of molecular events has led to the recent U.S. Food and Drug Administration (FDA) approval of several targeted therapies for improving the care of patients with AML. Currently, 60–70% of adult AML patients achieve complete remission after initial induction chemotherapy, and more than 25% of adults with AML are expected to survive 3 or more years and may be cured.[1] However, relapsed disease and treatment-related complications, mainly infections, are the most common causes of death. Following the concepts of personalized medicine, targeting the microbiota in a metabolite-dependent manner offers a novel adjuvant treatment approach that can improve treatment outcomes.

Microbiome

Microbiota is a diverse consortium of microorganisms that inhabit a defined environment. Along with its genomes, structural components, metabolites, and environmental factors, which are referred to as the microbiome, the microbial community residing in humans plays a critical role in host physiology.[2] The GM is considered the most significant microbiota in maintaining our health, but a variety of microorganisms are also localized in other regions, including the oral cavity, lungs, vagina, and skin. The microbial communities are in symbiosis with the host, contributing to the maintenance of tissue homeostasis, the integrity of mucosal epithelial barriers, immune system development, tolerance and response, protection of pathogen resistance, and modulation of inflammation. The human GM has crucial functions to digest foods and uptake nutrients.

Reduced diversity and altered composition of the microbiota, named dysbiosis, may directly cause disease or merely reflect disease-induced changes in the host immune and metabolic systems. Several established examples of changes in the GM have been associated with cardiovascular, neurological, metabolic, and inflammatory diseases, as well as all stages of cancer, including initiation, progression, treatment outcomes, and adverse reactions. In recent years, increasing evidence has confirmed the effect of the GM on pathological changes in hematological malignancies. Previous studies have revealed the remarkable reduction of GM diversity in AML patients, with significant differences in relative abundances of exact taxa in comparison to healthy controls.

The composition of the GM, as well as its dynamic changes, are individual for each person and are influenced by heredity, environment, lifestyle, and other factors. In the unique clinical scenario of AML patients, several factors, including prolonged hospitalization, multiple

Table 1. Examples of microbiota-derived metabolites and their functions in the host organism

Groups	Metabolites	Microbial agent	Functions	References
Short-chain fatty acids	acetate, propionate, butyrate, valerate, isobutyrate, isovalerate, 2-methylpropionate, hexanoate	Bacteroidetes (*Bacteroides sp*, *Prevotella*), Firmicutes (*Staphylococcus aureus*, *Coprococcus*, *Clostridium*, *Roseburia*, *Faecalibacterium*, *Eubacterium*, *Blautia*), Proteobacteria (*Campylobacter jejuni*), Actinobacteria (*Bifidobacterium sp.*), Verrucomicrobia (*Akkermansia muciniphila*)	host metabolic pathway regulation; inflammatory response regulation; local and systemic immunomodulation; maintenance of energy homeostasis; gut hormone production; microbiota composition regulation; defence against pathogens; maintenance of gut barrier integrity; intestinal permeability regulation; anticancer activity	3–9
Tryptophan and indole derivatives	indole, indole-3-propionic acid, 5-hydroxyl indole, indoxyl sulfate, N-acetyltryptophan, indoxyl sulfate, serotonin, melatonin, melatonin 6-sulfate	Firmicutes (*Lactobacillus spp.*, *Clostridium*), Actinobacteria (*Bifidobacterium*), Bacteroidetes (*Bacteroides*), Proteobacteria (*Escherichia coli*, *Shigella*)	host metabolic pathway regulation; inflammatory response regulation; local and systemic immunomodulation; antioxidative functions; neuroprotection and cytoprotection; intestinal barrier regulation	10–12
Bile acid metabolites	cholic acid, deoxycholic acid, chenodeoxycholic acid, taurocholic acid, lithocholic acid, glycocholic acid, ursodeoxycholic acid	Actinobacteria (*Bifidobacterium*), Bacteroidetes (*Bacteroides*), Firmicutes (*Clostridium*, *Lactobacillus*), Proteobacteria (*Enterobacter*)	host metabolic pathway regulation; antimicrobial effects; intestinal barrier regulation	13,14
Choline metabolites	TMA, methylamine, dimethylglycine, dimethylamine	Firmicutes (*Faecalibacterium prausnitzii*), Proteobacteria, Actinobacteria (*Bifidobacterium*), Bacteroidetes (*Prevotella*), Fusobacteria (*Fusobacterium*)	pro-inflammatory response promotion; mitochondrial dysfunction exacerbation; cell membrane function regulations; neurotransmission; lipid metabolism and biosynthesis regulation	15
Vitamins	vitamin B2, vitamin B3, vitamin B5, vitamin B6, vitamin B9, vitamin B12, vitamin K	Actinobacteria (*Bifidobacterium*), Firmicutes (*S. aureus*, *Listeria. monocytogenes*, lactic acid bacteria, *Salmonella typhimurium*)	cellular metabolism regulation; immunomodulation; antimicrobial effects; DNA replication, methylation and repair	16

antibiotic administrations, gastrointestinal mucosal damage, and severe immune system and nutrition impairments, cause disruptions of the GM to a level rarely seen in other clinical conditions.

Recently, host–microbiome interactions via microbial metabolites have become a great area of interest in terms of the defining underlying mechanisms that connect the microbiota with particular changes in host physiology. The complete set of small molecules, including intermediate or end products of bacterial metabolism, termed the metabolome, is suspected to be a strong contributor to our health via constant inter-organ interactions. When the gut barrier is compromised, tissues and organs may be flooded with molecules from the diet and microbiota that negatively or positively impact the host immune system and metabolism. On the other hand, the feedback loop can modulate the micro-ecological balance.

Undigested foods reach the colon and serve as substrates for bacterial metabolism. Carbohydrates, proteins and fats, the major macronutrients, provide different microbiota-accessible nutrients to generate the synthesis of vitamins, short-chain fatty acids (SCFAs), essential amino acids, and secondary metabolites. Indigestible dietary carbohydrates select fiber-degrading, SCFA-producing bacteria, which are considered to be beneficial under normal conditions. Undigested proteins promote the growth of proteolytic bacteria connected with SCFAs, branched-chain fatty acids and some toxic metabolites, including ammonia and hydrogen sulfide. Conjugated fatty acids are the main source of fat for bacterial metabolism. Overgrowth of acid-tolerant bacteria produces toxic compounds like hydrogen sulfide. Detailed and mechanistic knowledge about microbiome–host signaling pathways in AML is limited, even though progress has been made recently.

To date, most studies investigating a potential link between the fecal microbiome and AML have focused on microbiota-derived SCFAs, such as acetate, propionate and butyrate. In particular, a reduction in fecal SCFA concentrations has been observed, while investigation of SCFA levels in serum or plasma has led to more conflicting results. An increasing body of evidence now points to a potential role of different microbiome-derived components, such as lipopolysaccharides derived from bacterial cell walls, tryptophan-related metabolites, choline metabolites, secondary bile acids, and others, in the modulation of AML course (Table 1).[3–16]

Metabolomics

Metabolomics is a branch of "omics" sciences that aims to identify small molecules in a given sample, such as body fluids or tissues, for in situ analysis of metabolic changes. When combined with genetic, protein expression and

analytical tools, this approach is a powerful tool for characterizing the enzymatic and metabolic activity of cellular pathways.[17] The overarching goal of metabolomics is to assess these metabolites quantitatively and qualitatively for their diagnostic, therapeutic and prognostic potentials.

Due to the highly heterogeneous and dynamic nature of the metabolome, its characterization in the framework of different host–microbiome interactions is challenging. Bacterial metabolomes are thought to be composed of a few thousand metabolites, including more conserved products of core metabolism and energy production (nucleotides, amino acids, tricarboxylic acid cycle intermediates, glycolysis, and the pentose phosphate pathway) and arising from secondary metabolism.[17,18] Currently, research uses an untargeted approach to identify all small molecules, which requires complex methodological and analyzing protocols. To capture metabolites of interest, targeted metabolomics offers more straightforward tools.[19]

The metabolome has been extensively investigated to identify characteristic signatures in many diseases. Specific metabolic profiles have also been associated with the different stages of AML patient management.[20–22] Uncontrolled growth and proliferation of neoplastic cells result in a wide spectrum of metabolic disturbances reflected in leukemic cell metabolism directly (single cell metabolomics) but also in the bone microenvironment, blood and other biological specimens. In AML settings, there is a wealth of literature concerning metabolic alterations in the context of oncogenic mutations and epigenetic modifications.[23] However, the complexity of AML's issues, from diagnosis to completion, is influenced by more sophisticated interactions at different levels. The metabolic activities of the GM form an essential part of this machinery. Recent studies have focused mainly on fecal metabolites; therefore, a large-scale analysis of the relationship between microbes and the metabolic profiles of various tissues in an organism needs to be developed to provide consistent and comprehensive characterization of AML metabolic disturbances.

Does the microbiome drive AML?

Along with genetic and environmental factors, microorganisms have been reported as the next leading carcinogens, responsible for approx. 20% of human neoplasms.[24] The existence of selected microorganisms can modulate tumorigenesis via numerous mechanisms. At distant locations in the body, these effects are determined by the circulation of microbiota-dependent activated or suppressed immune cells, cytokines and metabolites. These last can play a critical role as cancer promotors or inhibitors. The oncogenic mechanisms of these complex connections have not yet been fully clarified.

Directly, microbiomes can produce toxic or carcinogenic compounds that modify cellular processes and initiate signaling actions to control cell growth. Some products of bacterial metabolism, such as microbial catabolism of dietary proteins, polyamines, xenobiotics, or aromatic amino acids, can induce tumor expansion through oxidative stress and DNA instability.[25–27] Indirectly, they are involved in the development and regulation of the immune system, a basic anti-tumor tool in the human body. There is evidence in favor of the role of the microbiota in the development and regulation of B lymphocytes, T helper lymphocytes and tolerogenic dendritic cells. Both commensal bacteria and their metabolites, such as butyric acid, are necessary for the development of regulatory T cells.[28,29]

A growing body of research has applied metabolomics techniques to identify metabolites from different sample sources associated with AML pathogenesis. However, there is a lack of data on mechanistic insight into metabolite-induced changes in specific pathways. Among the most extensively studied, microbial-originated butyrate plays a multilevel role in AML pathogenesis and outcomes. Specifically, it activates suppressive regulatory T cells, reduces the proinflammatory pathway of NF-kB, stimulates G-protein-coupled receptors 41 and 43, influences gene expression in cell growth and death at the epigenetic level, and aids in the barrier function of the epithelium, increasing the number of formations of tight junction proteins through the modulation of AMP-activated protein kinase.[30–33] Propionate, another SCFA, can promote ferroptosis and apoptosis through mitophagy and ferroptosis mediated through acyl-CoA synthetase long-chain family member 4. This elicits anti-leukemia immunity in AML. Recent results showed that decreased levels of propionate in the feces of AML patients correlated with GM dysbiosis. Propionate suppressed AML progression both in vivo and in vitro. Acyl-CoA synthetase long-chain family member 4-induced ferroptosis increased the immunogenicity of AML cells, induced the release of damage-associated molecular patterns, and promoted dendritic cell maturation.[34]

Currently, using a variety of statistical tools or advanced computational methods, studies are focused on the generation of paired metagenomic and metabolomic features from the AML cohort to determine potential diagnostic profiles correlated with leukemia onset, progression and relapse. In a comprehensive study, Wang et al. explained the role of microbiomes in AML progression in a metabolite-dependent manner. Antibiotic treatment-induced dysbiosis, a decrease in butyrate produced by the GM (especially *Faecalibacterium*), and the increased leakage of lipopolysaccharides through the damaged intestinal barrier into the blood accelerate AML progression.[35] As single-type samples may not fully reflect overall changes in organismal metabolism, Wu et al. investigated the differences in the metabolome of human blood and mice serum, liver and feces under conditions of AML. Significant differences in the serum and fecal metabolomes between the AML group and control group of mice successfully distinguished 2 different

profiles. Metabolic changes associated with AML primarily affect amino acid and glucose metabolism. Through cross-species validation, the study discovered the potential involvement of the carnosine–histidine metabolic pathway in the development and progression of AML. Analysis of the GM showed a significant negative correlation between the key metabolite carnosine and *Peptococcaceae* and *Campylobacteraceae*. Finally, a significant decrease in indole levels observed in mouse feces may contribute to the development of AML via weakened immune surveillance ability and exacerbation of intestinal inflammation.[36]

Increasing attention to the pathogenic relationship between the microbiome and AML development in experimental and clinical studies has been drawn recently. However, considering the complexity of the connections between host metabolism, inflammation, immune responses, and hematopoiesis, many open questions remain to be explored.

Treatment and microbiome changes

The condition of AML patients is deeply complicated by the large number of factors influencing microbiome composition, which often makes it impossible to distinguish whether changes in microbiome composition are caused by a disease or causally involved in its pathogenesis.

Antibiotics

Emerging evidence suggests that antibiotic therapy leads to a reduction in microbiota diversity, promotion of antibiotic-resistant organisms, and disruption of the mucosal barrier function, consequently resulting in recurrent *Clostridioides difficile* or systemic infections, as well as alterations in its metabolic activity. Bacterial taxa responsible for essential metabolic functions, such as butyrate production, have been shown to decrease after just 7 days of broad-spectrum antibiotics. Beta-lactams and metronidazole, targeting obligate anaerobes in the gut, exacerbate this effect.[37]

Nutrition

Nutrition is one of the most fundamental factors in maintaining a balanced human GM for patients undergoing leukemia therapy. In a mouse study, caloric restriction led to changes resembling those observed after cytotoxic therapy, including expansion of *Akkermansia* and *Bacteroides*, reduction of *Bacilli*, mucin glycan degradation with mucus layer thinning, decreased levels of acetate, propionate and butyrate, and elevated succinate concentrations.[38] In a small non-randomized study, in contrast to parenteral nutrition (PN), enteral nutrition (EN) was found to expedite the recovery of microbiome diversity, composition and SCFA production post-transplant in pediatric patients.[39] Enteral nutrition exerts a trophic effect on the gut epithelium, providing essential nutrients for SCFA producers. Despite total PN being commonly utilized to enhance the nutritional status of graft-versus-host disease (GVHD) patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT), EN is currently the preferred mode of nutritional support in cancer patients.[40] The adverse effects of parenteral feeding arise from impaired gut-associated lymphoid tissue function, including compromised adaptive immune cells, intestinal epithelium damage, alterations in metabolic product profiles, and changes in the intestinal microbiome. These factors collectively heighten susceptibility to infections.[41] Conversely, EN-enhanced SCFA production shields against intestinal mucosal atrophy and bacterial translocation.[42–44] A pilot study examining the effects of nutrition on post-allo-HSCT GM found that PN was less effective than EN in maintaining microbiota diversity and composition. Patients receiving EN showed higher levels of *Faecalibacterium* and *Ruminococcus E bromii*, while prolonged minimal oral intake reduced microbial diversity and decreased SCFA-associated taxa, such as *Faecalibacterium prausnitzii* and *Blautia*. These findings support the preference for EN over PN in allo-HSCT patient care.[45]

Chemotherapy

An expanding body of research on acute leukemia patients has demonstrated a chemotherapy-induced adverse influence on intestinal barrier integrity, permeability and GM condition. Apart from notable differences in GM profiles, chemotherapy-treated patients exhibit diverse metabolite profiles. Reduced diversity and pathological composition of the GM translate directly to metabolic alterations that can potentially persist in survivors.[46–51]

Rashidi et al. provided patient- and sample-level longitudinal GM and circulating microbiome data from AML patients hospitalized to receive induction chemotherapy. They showed a decrease in alpha diversity and a decline in citrulline (a marker of functional enterocyte mass) until approx. day 12, followed by a slow rise toward baseline. A significant association between 11 genera of the GM and 201 serum metabolites formed 2 distinct patterns. The 1st group of genera contained obligate anaerobic commensal genera in the Clostridia class. Metabolites were enriched in amino acid and xenobiotic pathways and included known microbial metabolites of dietary tryptophan and tyrosine, as well as butyrate/isobutyrate. Frequently pathogenic species, including *Enterococcus*, *Pseudomonas*, *Rothia*, and *Veillonella*, contributed to metabolites connected with the lipid pathway in the 2nd group.[52] The profiles of the GM and metabolites in AML patients with and without chemotherapy and control individuals were

compared by Xu et al. Patients with AML presented an increased ratio of Firmicutes to Bacteroidetes. *Collinsella* and *Coriobacteriaceae* were significantly enriched in newly diagnosed AML patients, serving as AML biomarkers. Plenty of bacteria showed correlations with specific amino acid expressions. Among them, both *Collinsella* and *Coribacteriaceae* were linked to fecal hydroxyprolyl-hydroxyproline, prolyl-tyrosine and tyrosyl-proline.[53] Hueso et al. linked induction chemotherapy (7+3 regimen) to intestinal barrier injury, reflected by a decrease in citrulline levels and significant loss of overall bacterial load and alpha and beta diversities, with a switch from anaerobic to aerotolerant bacteria. Gut impairment was associated with a reduction in fecal SCFAs, which mirrors its necessity in colonocyte support, crypt depth regulation, mucus secretion, tissue homeostasis maintenance, and intestinal repair.[54] Pötgens et al. recently investigated the links between GM changes and cachectic features in AML patients using a multi-omics approach, including fecal, blood and urine metabolome assessment. They observed that intensive treatment led to elevated systemic inflammation, muscle mass depletion, anorexia, and weight loss, along with transient impairment of gut barrier function and persistent alterations in GM composition marked by reduced diversity. At the end of the induction, *Lactobacillaceae* and *Campylobacter* levels increased, whereas 3 SCFA producers (*Intestinibacter bartlettii*, *Odoribacter splanchnicus* and *Gemmiger formicilis*) were reduced. Contrarily, *Enterococcus faecium* and *Staphylococcus* levels were increased at discharge. Metabolomics analyses indicated persistent reductions in urinary hippurate and fecal bacterial amino acid metabolites (2-methylbutyrate, isovalerate and phenylacetate).[55] New modalities, such as CPX-351, a liposomal cytarabine plus daunorubicin combination, approved for adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes enhanced survival compared to the 7+3 regimen. In preclinical models, CPX-351 averted mucosal damage, dysbiosis and morbidity by activating the aryl hydrocarbon receptor–IL-22–IL-10 host pathway and generating immunomodulatory metabolites by anaerobes.[56]

The bidirectional interplay between the microbiome and anticancer chemotherapy is significant. Gut microbiota and microbial metabolites influence both the effectiveness and adverse effects of chemotherapeutics, including immunotherapy. This relationship is further underscored by the concept of pharmacomicrobiomics, where microorganisms can also alter the biotransformation of drugs, affecting their bioavailability, bioactivity and toxicity through metabolites. Moreover, due to their anti-tumor activity, microbial-derived metabolites possess the property to exert the tumoricidal effect of conventional therapeutics. For example, sodium butyrate, a histone deacetylase inhibitor, enhances the efficacy of venetoclax against AML cells through an increase in apoptosis induction.[57] The combination of sodium butyrate with exogenous recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has demonstrated enhanced antiproliferative effects in leukemia cells harboring the t(8;21) translocation. TRAIL, a member of the tumor necrosis factor (TNF) cytokine family, functions in immune surveillance and selectively induces apoptosis in various cancer cells. Histone deacetylase inhibitors upregulate TRAIL receptor expression, increasing the susceptibility of target cells to TRAIL-induced apoptosis. In leukemia cells with the t(8;21) translocation, TRAIL expression is diminished, making the combination of sodium butyrate and recombinant TRAIL a promising therapeutic strategy for the clinical management of t(8;21) AML.[58]

Neutropenic fever

Dysbiosis is intricately linked to infectious complications, which represent a prevalent cause of mortality among patients with hematologic malignancies. Neutropenic fever (NF) is a common clinical exacerbation, but its clear etiology usually cannot be found.

Recent evidence indicates a link between the microbiota and NF occurrence in AML patients. Rashidi et al. identified a shift in circulating metabolites after NF, of which 13 were associated with the GM. The level of metabolites contributing to intestinal epithelial health (citrulline) and bacterial metabolites of dietary tryptophan (indole) with known anti-inflammatory and gut-protective effects decreased after NF in parallel with an increase in mucolytic and a decrease in butyrogenic bacteria.[59] To better understand NF pathogenesis, the authors profiled the GM in 2 cohorts of patients with acute leukemia and showed that mucolytic species, *Akkermansia muciniphila*, expansion in the gut was associated with an increased risk for NF. Serum metabolites involved in the γ-glutamyl cycle, known oxidative stress mediators, correlated both with *A. muciniphila* and NF. Moreover, the level of gut microbial-derived indole compounds increased after *A. muciniphila* expansion and decreased before NF, suggesting their anti-inflammatory effects. This study suggests that NF relies on the pyrogenic and inflammatory effects of metabolites absorbed from the gut, and compromised mucolytic function of *A. muciniphila* is crucial in this process.[60] Similar studies on allo-HSCT patients with AML have yielded consistent evidence of the relationship between *A. muciniphila* and NF. In addition, irradiation, melphalan and caloric restriction increased the relative abundance of *A. muciniphila*. Moreover, caloric restriction of unirradiated mice reduced acetate, propionate and butyrate. Treatment with an antibiotic targeting *A. muciniphila* or propionate supplementation in mice preserved the mucus layer. These results suggest that there are comprehensive interactions between diet, metabolites, colonic mucus, and the microbiome in NF risk.[38]

Microbiota-based approaches

Nutrition

Nutritional status significantly influences the outcomes of leukemia patients. Both malnutrition and obesity induce changes in the GM and alter the production of detrimental bacterial metabolites, which implies negative effects.[61,62] Muscle mass serves as an independent factor in post-HSCT survival. The GM and its metabolites play a role in regulating metabolism, affecting skeletal muscle mass and function. A study implementing soy–whey blended protein in HSCT patients demonstrated improved muscle strength and area, along with increased GM alpha-diversity. Lack of response was associated with a reduction in butyrate-producing taxa, while taxa such as *Ruminococcus* and *Veillonella* showed positive correlations with muscle status. Furthermore, the group that responded positively to the intervention exhibited characteristics related to amino acid biosynthesis and the pentose phosphate pathway, both crucial for the anabolic processes involved in skeletal muscle regeneration.[63]

Route of feeding

The documented role of EN in maintaining GM homeostasis resulted in its recommendation by main international guidelines. When comparing EN to total PN in 20 pediatric post-HSCT patients, the EN cohort exhibited rapid recovery of microbiome diversity, composition and SCFA production after transplantation. This was characterized by the restoration of *Faecalibacterium*, *Dorea*, *Blautia*, *Bacteroides*, *Parabacteroides*, and *Oscillospira*.[39]

Diet

Disease-related alterations in eating habits and nutritional protocols among leukemia patients can lead to a depletion of dietary fiber, an essential nutrient for the GM. Significantly, Maia et al. conducted a study comparing the microbiological and nutritional composition of neutropenic and regular diets, revealing comparable microbial loads but decreased fiber and vitamin C content in the strict neutropenic diet.[64] Restriction of fruits and vegetables can disrupt the balance of the GM and increase the risk of bacterial overgrowth and translocation. Under conditions where dietary accessible substrates are limiting, host mucins serve as a source for microbial fermentation, promoting gut barrier injury. Given insufficient evidence supporting the beneficial effects of a low-bacterial diet on infection and mortality in neutropenic patients, a standardized approach focused on the safe handling of foods serves as a promising alternative to a restrictive diet.

Probiotics

Among cancer patients, the utilization of dietary and commercial probiotic supplements is becoming more common, but data are limited regarding the impact of probiotics on the microbiome in acute leukemia. In murine models of allo-HSCT, Sofi et al. demonstrated that administering a single strain of commensal bacteria, *Bacteroides fragilis*, led to increased GM diversity and an abundance of beneficial commensal bacteria, effectively alleviating the development of acute and chronic GVHD. The mechanism underlying this improvement was linked to elevated levels of SCFAs, interleukin 22 (IL-22) and regulatory T cells, which contributed to enhanced tight junction-related gut integrity and reduced production of inflammatory cytokines by pathogenic T cells.[65] Considering the limited efficacy of single selective probiotic supplementation in restoring AML-related dysbiosis, probiotic cocktails are being explored as alternative strategies. In one study, oral administration of a selected mixture of 17 butyrate-producing Clostridia strains to adult mice improved gut epithelial integrity, reduced GVHD severity and improved survival.[66]

The recent live biotherapeutic products category of drug products relating to living organisms with notable effects on diseases has been designed by FDA to clarify pharmaceutical expectations.[67] *Clostridium butyricum* MIYAIRI 588 (CBM588), a spore-forming anaerobic bacterium, has been categorized as a live biotherapeutic product. In a prospective observational study, prophylactic CBM588 contributed to the preservation of intestinal microbiota diversity. Specifically, it significantly increased the abundance of *C. butyricum* while reducing cluster III microbiota early after HSCT.[68] An ongoing phase I clinical trial (NCT03922035) is evaluating the safety and tolerability of administering *C. butyricum* CBM 588 Probiotic Strain during HSCT (from day +1 to +28), with secondary outcomes including analysis of GM changes.

Prebiotics

Prebiotics, defined as "substrates selectively utilized by host microorganisms, conferring health benefits", encompass fermentable, non-digestible carbohydrates metabolized by specific commensal bacteria in the colon.[69] Unlike probiotics, which contain live microbes, prebiotics are non-living nutrients present in both food and supplements. These include inulin, fructo-oligosaccharides, xylo-oligosaccharides, galacto-oligosaccharides, potato starch, conjugated linoleic acid, polyunsaturated fatty acids, human milk, phenolics, phytochemicals, and other readily fermentable dietary fibers. Administration of prebiotics significantly promotes beneficial groups of bacteria, especially SCFA producers, by providing them with essential substrates for microbial fermentation.[70,71] Riwes et al. have successfully

demonstrated that prebiotic treatment with resistant starch in patients with allo-HSCT was feasible and promoted butyrogenic microbiota, increasing levels of intestinal butyrate in longitudinal observation.[72] Future studies investigating prebiotic supplementation that include the measurement of circulating SCFA concentrations are warranted.

Postbiotics

Given the potential infection risk associated with probiotics and the requirement of a healthy gut microbial community for prebiotic digestion, postbiotics have emerged as a potentially safer and more efficient approach. Postbiotics encompass functional bioactive components derived from inactivated microbial cells or their constituents, often supplemented with metabolites.[73] In vitro and murine model studies have elucidated numerous beneficial effects of postbiotics, notably encompassing the preservation of the gastrointestinal tract barrier surface, the modulation of intestinal epithelial cell damage, and the regulation of innate and adaptive host immune responses.[74] Short-chain fatty acids, particularly butyrate, stand out as the most extensively researched postbiotics. In a leukemia setting, local delivery of exogenous butyrate has been shown to enhance the integrity of intestinal epithelial cell junctions, reduce apoptosis and alleviate GVHD in murine models, akin to the effects observed with 17 carefully selected strains of Clostridia known for their high butyrate production.[75] In addition to butyrate, propionate, another SCFA, has been found to protect intestinal epithelial cells and reduce acute GVHD severity, possibly through GPR43-mediated ERK phosphorylation and NLRP3 inflammasome activation.[76] Based on their unique characteristics and superior safety, postbiotics should be considered as a novel strategy for the improvement of outcomes of AML patients at all stages of therapy.

Fecal microbiota transplantation

The transfer of fecal material from healthy donors into the gastrointestinal tract of recipients, named fecal microbiota transplantation (FMT), imparts beneficial changes in both the microbial community and in metabolic profiles. Growing interest in the application of FMT in various clinical settings has led to its increasingly extensive use in the field of hematology with a great future. Fecal microbiota transplantation, being the ultimate probiotic, has provided clinical benefits to recipients of HSCT. The experience of recent years has shown a number of advantages of FMT in different indications, including restoration of dysbiotic microbiota, prevention of severe infections through eradication of antibiotic-resistant bacteria, treatment of GVHD, and prevention and treatment of *Clostridium difficile* infection.[77–80] The risk of infection associated with the procedure remains the biggest concern of applying FMT to highly immunosuppressed patients with hematologic conditions. Therefore, despite the currently encouraging results in terms of efficacy and safety, following the actual recommendations, FMT is indicated only for the 2nd recurrence of *C. difficile* infection.[81] To avoid recipient exposure to potentially pathogenic foreign microorganisms, Taur et al. investigated the administration of autologous FMT, harvested before obtaining the restoration of microbiota diversity and composition to pre-transplant levels with *Lachnospiraceae*, *Ruminococcaceae* and *Bacteroidetes*, in a treatment arm only.[82] Novel strategies for customizing the composition of FMT to specific recipients and developments in the fecal inoculum preparation processes may improve the safety and efficacy of the procedure. The infusion of selected bacteria via synthetic bacterial suspension, defined as "bacterial consortium", with particular emphasis on SCFA producers, offers another potential solution.[83] Promising clinical outcomes encourage further evaluation of the use of FMT in AML settings with a special focus on its metabolic and immune effects.

Gut decontamination

Assuming that non-absorbable antibiotics can debulk intestinal bacteria and, therefore, decrease bacteremia and acute GVHD risk, some clinical centers practice gut decontamination (GD) in the peri-HSCT period. The rationale for this procedure is mainly based on promising results from murine, early single-arm, retrospective studies, while more recent research has presented varied results.[84–87] In a prospective, randomized study, GD with vancomycin and polymyxin B did not affect Shannon diversity or clinical outcomes but decreased the prevalence or abundance of gut pathogens and bloodstream infections (BSIs).[88] By comparing 2 decontamination schedules, Weber et al. did not show a difference in rates of infectious complications between ciprofloxacin/metronidazole and rifaximin; however, rifaximin tended toward higher intestinal microbiota diversity along with enhancement of antibiotic-induced dysbiosis.[89] Due to the lack of evidence supporting a clear benefit of this procedure and a proven link between the use of some antibiotics and dysbiosis, current guidelines do not recommend GD as a standard practice; however, a precise understanding of the correlation between specific bacterial strains and AML patient outcomes may change our approach to this procedure. While broad-spectrum antibiotics that attack non-specifically may exacerbate gut dysbiosis, the use of antibiotics with a spectrum narrow enough to target a specific negative bacterial species and spare beneficial ones may induce favorable efficacy. Moreover, pretreatment profiling of the individual gut microbiome composition may help facilitate decisions regarding the proper choice of antibiotics. Future studies incorporating modern multi-omics approaches are needed to explore the specific impact of different antibiotics on the GM and clinical outcomes.

Discussion

Future directions

As the GM is a complex ecological system that requires community collaboration, the administration of a single microbial strain alone may be ineffective. Holistic reshaping of the composition of the keystone consortium of microbes could be a promising approach. Precise microbial engineering technologies, including various CRISPR/Cas systems, offer a comprehensive tool to produce higher yields of bioactive metabolites and improve safety. Accurate delivery of engineered bacteria to the target area is the main challenge, and the use of an encapsulation system is being investigated as one of the possible solutions.

Based on the current results of preclinical research on the role of microbial metabolites in AML, a novel concept of postbiotics represents a promising alternative or complementary option to improve therapeutic response, mitigate treatment-related toxicity, protect against infectious complications, and even prevent disease progression. Postbiotics refer to bioactive compounds, cell fractions or metabolic products of bacterial origin. In the absence of live microorganisms, postbiotics administration may eliminate the risks of potential infections, providing a safer solution compared to probiotics or FMT. The lack of standardization in terms of formulation, optimal dosage, duration, and route of administration poses challenges in determining the best clinical implementation. Therefore, prebiotics, probiotics and postbiotics are still only classified as health products rather than medicines, and regulatory rules limit their application in the medical field. The safety of these microbiome-based interventions is a critical consideration in immunocompromised patients and represents the main objective of ongoing trials. Furthermore, individual variability due to dynamic differences in the GM during treatment necessitates microbiome profiling in accordance with the assumptions of next-generation personalized medicine.

Considering the unique and multiple mechanisms of action of microbiota-derived metabolites, they provide an opportunity to overcome the limitations of current traditional medicines, including risks of adverse reactions, interactions, tolerance, and dependence, and they may reduce reliance on antibiotics, leading to lower healthcare costs. A better understanding of the complex interactions between the GM and host health will facilitate breakthroughs in innovative treatments that hold the potential to transform the coming face of medicine. Promising results from small preliminary studies highlight opportunities for future research.

Limitations

The lack of available or reliable prior research considering microbial metabolomics in the context of AML is the main limitation of this review. Despite significant progress in understanding the role of microbial metabolites in many diseases, AML settings remain an open area for research. It is worth noting that in most of the above-discussed studies, patients with a diagnosis of AML represented only a small percentage of the total study group. Considering the unique metabolic profile of patients with leukemia, conditioned by the circumstances of the individual's health, the nature of the disease and the implications of treatment, current findings on the mechanistic role of microbial metabolites from different conditions cannot be directly applied to the context of AML. Future randomized clinical trials should be extended to include a larger sample and eliminate the influence of disturbing factors. Our paper does not provide a comprehensive discussion of mixed methods research, which involves combining different data collection methods in a single study. There are currently insufficient validated algorithms for use in clinical practice. In this case, various methods, including multi-omics-based strategies, should be applied more widely for a more effective understanding and investigation of microbiome-related changes in AML.

Conclusions

Metabolomics is becoming a dominant player in the functional assessment of AML issues, and it provides a novel perspective on our insight into its pathogenesis. Understanding the nature of the microbiome has direct translational importance, as microbial-derived products are both targets and modifiers of AML processes. In the future, microbial metabolic patterns may provide non-invasive biomarkers for early diagnosis, risk stratification, relapse prediction and detection, and even the identification of patients more likely to respond to treatment. Current personalized therapeutic approaches in AML are based on identifiable and targetable genomic lesions. Targeting specific individual microbiome-related features emerges as the next opportunity for therapeutic interventions. Ongoing efforts focusing on standardization in laboratory techniques and analysis are likely to result in the widespread adoption of metabolomics technology in clinical settings. Future efforts are needed to implement an integrative functional multi-omics approach in AML patient management. Despite treatment progress, addressing microbial metabolite challenges remains a crucial area for ongoing study and improvement.

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