Emerging Roles for the Gut Microbiome in Lymphoid Neoplasms

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ABSTRACT: Lymphoid neoplasms encompass a heterogeneous group of malignancies with a predilection for immunocompromised individuals, and the disease burden of lymphoid neoplasms has been rising globally over the last decade. At the same time, mounting studies delineated a crucial role of the gut microbiome in the aetiopathogenesis of various diseases. Orchestrated interactions between myriad microorganisms and the gastrointestinal mucosa establish a defensive barrier for a range of physiological processes, especially immunity and metabolism. These findings provide new perspectives to harness our knowledge of the gut microbiota for preclinical and clinical studies of lymphoma. Here, we review recent findings that support a role for the gut microbiota in the development of lymphoid neoplasms and pinpoint relevant molecular mechanisms. Accordingly, we propose the microbiota-gut-lymphoma axis as a promising target for clinical translation, including auxiliary diagnosis, novel prevention and treatment strategies, and predicting clinical outcomes and treatment-related adverse effects of the disease in the future. This review will reveal a fascinating avenue of research in the microbiota-mediated lymphoma field.

KEYWORDS: Gut microbiome, lymphoid neoplasms, microbiota-gut-lymphoma axis, dysbiosis, carcinogenesis, biomarker

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Introduction

Lymphoid neoplasm, a highly heterogeneous malignancy characterized by diverse levels of immune dysregulation, is well classified as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL),[1] which has presented a persistently increasing incidence with the transformation of population age structure and population growth in recent years.[2] However, despite many advances in the understanding of the pathogenesis and the clinical intervention of the disease, the pathogenesis of lymphoid neoplasms is far from being clarified, and effective treatment for relapses and/or refractory disease remains a tremendous challenge, and many patients succumb to their disease.[3,4] Therefore, understanding the factors that contribute to this malignant behaviour and developing optimal biomarkers and targets for clinical application are urgently needed.

Trillions of microbes inhabit many parts of the human body, including the gastrointestinal tract (GIT), skin, oral mucosa, and conjunctiva. The vast majority of commensal bacteria reside in the colon,[5] consistent with the most prominent site of isolated lymphoid follicles induced by certain gut flora, which are key players in the equilibrium between the gut flora and the immune system.[6] During the past decade, accumulating evidence has demonstrated that the gut microbiota has a close association with various human diseases, such as inflammatory, autoimmune, metabolic, neoplastic, and neurodegenerative diseases.[7-10] There is a large potential for the intestinal microbiome to impact a multitude of human physiological functions, including immune homeostasis, inflammatory response, and host metabolism,[11-14] which might account for the potential pathogenesis of these diseases. In addition, approximately 13% of the global cancer burden can be attributed to certain carcinogenic pathogen infections,[15] and *Helicobacter pylori* infection with gastric mucosa-associated lymphoid tissue (MALT) lymphoma constitutes an example of microbiota-driven malignancy. Remarkably, with the recent development of culture-independent technologies, alterations in the structural composition and/or function of the gut microbiome that lead to detrimental effects on the host, also known as intestinal dysbiosis, have recently been increasingly revealed to be associated with the genesis of a subgroup of lymphoid neoplasms. Thus, the human gut microbiome represents an intriguing reservoir of new therapeutic opportunities for lymphoid neoplasms (henceforth referred to simply as lymphomas), which supports our hypothesis that the microbiota-gut-lymphoma axis might emerge as a novel target for clinical translation.

In this review, we mainly discuss the possible roles of the gut microbiota in a range of lymphoma types, with an emphasis on unique pathogenic mechanisms and treatment opportunities, including assisting diagnosis, identifying a manageable target for clinical intervention, predicting therapeutic outcomes and therapy-related adverse effects, and future directions and current challenges for better knowledge of the microbiota-mediated lymphoma field.

Gut Microbial Dysbiosis Implicates a Range of Lymphoma Subtypes

The GIT is the most frequent primary extranodal site in lymphoma, and intestinal microbial dysbiosis has been well documented in patients with selective lymphoma subtypes. Of them, *H pylori* infection with gastric MALT lymphoma can be

Table 1. Major human gut microbiota studies in lymphoid neoplasms by 16S ribosomal RNA sequencing.

STUDIES	INDIVIDUALS (CASE VS CONTROL, N)	SAMPLE TYPES	AMPLIFIED REGIONS	PRIMARY FINDINGS
Cozen et al[26]	13 AYAHL survivors vs their unaffected twins	Faecal samples	V2	Modest reductions in the diversity of bacteria in AYAHL survivors
Rajagopala et al[27]	28 paediatric and adolescent patients with ALL vs 23 matched healthy siblings	Faecal samples	V1-V3	Significantly lower microbiota diversity; relatively lower abundance of *Anaerostipes, Coprococcus, Roseburia*, and *Ruminococcus2* in the patient group
Zeze et al[28]	20 patients with GI-FL vs 20 healthy controls	Duodenum mucosal biopsy samples	V4	Significantly lower alpha diversity; significantly lower abundance of *Sporomusa, Rothia* and *Prevotella* and the family *Gemellaceae* in patients with GI-FL
Bai et al[29]	30 patients with ALL vs 33 healthy controls	Faecal samples	V3-V4	Lower alpha diversity; the abundance of *Firmicutes* decreased and that of *Bacteroidetes* increased in patients with ALL
Chua et al[30]	73 adult survivors of childhood ALL vs 61 healthy controls	Faecal samples	V4	Reduced microbial diversity; enrichment of *Actinobacteria* (eg, genus *Corynebacterium*) and depletion of *Faecalibacterium* in cancer survivors

ALL: acute lymphoblastic leukaemia; AYAHL: adolescent/young adult Hodgkin lymphoma; GI-FL: gastrointestinal follicular lymphoma.

a paradigm. That is, more than 90% of patients with gastric MALT lymphoma are associated with *H pylori*–induced gastritis,[16] and lesions resembling human gastric MALT lymphoma have been shown to develop in mice with chronic *Helicobacter* infection, particularly those associated with *Helicobacter felis*.[17,18] Importantly, eradication of the infection with specific antibiotics will often lead to clinical remission.[19,20] In addition, microbial exposure early in life has long been suspected in the aetiology of childhood leukaemia, specifically acute lymphoblastic leukaemia (ALL).[21-23] Of note, the delivery mode has been regarded as one of the important environmental factors shaping the microbial flora in newborns.[24] Human life begins in the mostly sterile environment of the womb, and exposure to microorganisms initiates when the amniotic sac breaks, which is the first step in the introduction and transfer of maternal microbiota to the infant. In a recent population-based case-control study, an increased risk (odds ratio [OR], 1.52; confidence interval [CI]: 1.02-2.25) of infant ALL following caesarean delivery was identified,[25] suggesting that altered microbiota colonization might be implicated in the development of lymphoma in infants.

With remarkable advances in DNA sequencing technologies, a number of studies have begun to focus on the roles of the gut microbiota in certain lymphoma subtypes (Table 1).[26-30] Among them, Cozen et al[26] conducted a small case-control study to investigate the difference in faecal microbial diversity between survivors of adolescent/young adult HL and their unaffected twins via 16S ribosomal RNA (rRNA) sequencing, and they found modest reductions in bacterial diversity in the survivors, although further studies are needed to confirm this finding. In another matched cohort study,[27] the authors indicated that the microbiota diversity of paediatric and adolescent ALL groups was significantly lower than that of a control group, and a relatively higher abundance of *Anaerostipes, Coprococcus, Roseburia*, and *Ruminococcus2* was found in healthy controls, which revealed the possibility of distinguishing patients from control groups based on their microbiota profiles. Apart from the faecal microbiota, intestinal mucosal microbial dysbiosis in patients with gastrointestinal follicular lymphoma has been reported recently.[28] These findings highlight that disturbances of the gut microbiome might be involved in the pathogenesis of a subset of lymphomas, but caution should be taken when considering several confounding factors, including medical history and comorbidities of patients, as well as nonconformity of sample collection and data analysis methods among these studies.

Postulated Molecular Mechanisms for Gut Microbiota–Mediated Lymphoma

The gut microbiome contributes to oncogenesis through multiple steps and complex mechanisms, which has been broadly established in various tissues.[31] Similarly, lymphomagenesis is an intricate process influenced by both genetic and environmental factors. Herein, we shed light on select microbiota-associated components that are involved in the pathogenesis of lymphoma.

Aberrant activation of the immune system

Lymphoma comprises a large group of subtypes that arise from lymphoid tissues and directly involves the human immune system with a propensity in immunosuppressed individuals,[32,33] such as patients with AIDS, autoimmune disorders, and infection. The human immune system is responsible for distinguishing endogenous and exogenous non-pathogenic organisms and properly calibrating the responses to pathogens to maintain homeostasis and health.[34] The GIT provides a critical interface where crosstalk between the enormous number of

microorganisms and the host immune system takes place.[35] An array of innate immunocytes, including myeloid cells and innate lymphoid cells, can sense microbial antigens through pattern recognition receptors and then regulate the intestinal immune system by activating a downstream cascade of signalling molecules, such as components of the nuclear factor kappa B (NF-κB) pathway.[12] Noticeably, the gut microbial flora plays an essential role in the genesis of mucosal lymphoid structures.[36] Germ-free animals exhibit distinct hypoplastic Peyer's patches compared with those of specific pathogen-free animals that contain a simple flora.[37] In addition, in a murine model,[6] researchers demonstrated that peptidoglycans, deriving from intestinal gram-negative bacteria, can induce the formation of isolated lymphoid follicles through recognition by the nucleotide-binding oligomerization domain containing 1 (NOD1) expressed by epithelial cells, leading to the expression of 2 known ligands (β-defensin 3 and C-C motif chemokine 20) for the chemokine receptor CCR6.

Similar to the case for the innate immune system, sophisticated microbial modulations have been suggested to implicate the adaptive immune response.[34] Given that both B lymphocytes and T lymphocytes arise from haematopoietic stem cells (HSCs) in the bone marrow, one remarkable study of obese mice model[38] determined that alterations of the bone microenvironment were likely to be a result of gram-positive bacterial dysregulation. That is, compared with controls, mice in high-fat diet (HFD) exhibited maladjusted microbial compositions in cecum and ileum and aberrant bone marrow HSC niche with shifting mesenchymal stem cell differentiation into adipocytes by the activation of PPARγ2. Importantly, stool transplantation from HFD mice could transfer their HSC phenotype into normal mice, and depletion of gram-positive bacteria by vancomycin reversed the HSC phenotype observed in HFD mice. During the process of antigen selection, aberrant lymphocyte transformation might be driven by the continuous stimulation of microorganisms, which can trigger the development and expansion of selective lymphoma subtypes.[39] In low-grade primary B-cell gastric MALT lymphomas, *H pylori* induces clonal B lymphocyte expansion in vitro secondary to specific activation of T cells.[40] Collectively, infectious agents trigger chronic activation of the immune system and sustain a protracted proliferative status of lymphocytes. Eventually, neoplastic lymphoid transformation occurs.

Persistent inflammatory stimulation

The microbiota can confer both pro- inflammatory and anti-inflammatory responses, and inflammation might be a default immunological condition in defects of regulation.[35] A recent study of adult survivors of childhood ALL indicated that low-grade inflammation associated with higher levels of immune activation may be a result of maladaptive bacterial taxa.[30] Pathogen infection is the most common aetiology of inflammation, and the incidence of several malignancies can be attributed to infections.[41] It has been shown that the 4 most important pathogens for oncogenesis are *H pylori*, high-risk *human papillomavirus*, and *hepatitis B* and *C viruses*.[15] Among them, *H pylori* can trigger strong inflammatory responses by activating the NF-κB pathway[42,43] and inducing the expression of pro-inflammatory cytokines (the 2 best known are B-cell-activating factor of the TNF family [BAFF] and a proliferation-inducing ligand [APRIL]) to clear the infection in the gastric mucosa.[44-46] Persistent inflammation promotes the formation of mucosal lymphoid follicles, typically consisting of B lymphocytes, which might contribute to the genesis of gastric MALT lymphoma once the inflammatory courses are uncontrolled.[47] Interestingly, it has been reported that *H pylori* is linked with some other non-MALT lymphoma subtypes in the stomach,[48-50] and associations between *H pylori* infection and several diseases localized outside the stomach have been well reviewed.[51] The seemingly omnipotent *H pylori* fully testifies to the strength and complexity of the gut microbiome in human health.

The gut microbiota is a lavish source of molecules such as lipopolysaccharide and peptidoglycan that may result in inflammation in peripheral tissues of the body.[52,53] Similarly, inflammation can in turn increase the intestinal permeability that facilitates the entry of these inflammatory agents into the circulatory system, which leads to the formation of a vicious positive-feedback loop. The host immune system, however, can select for its microbial allies and secrete large quantities of IgA and antimicrobial peptides to exert protection from pathogenic organisms that cause infection.[34,54,55] In addition, short-chain fatty acids (SCFAs), representing a major class of metabolites produced by the metabolism of non-digestible carbohydrates,[11] might confer strong anti-inflammatory profiles via specific G protein–coupled receptors to promote homeostasis of the intestinal epithelium,[56] which play a crucial role in anti-carcinogenesis via exerting extracellular and intracellular effects, and the potential relationships between SCFAs and lymphomagenesis described below.[57]

Disturbances in intestinal and systemic metabolism

The gut microbiome is extensively related to both gut and host systemic metabolism, and associations between metabolites and microbial metabolic pathways are much higher than those between metabolites and species.[58] Importantly, the microbial inhabitants of the gut are increasingly considered an important environmental factor that contributes to a bulk of diseases by affecting metabolic processes, such as the metabolism of non-digestible carbohydrates, bile acids, and choline.[11] Most strikingly, SCFAs, mainly acetate, propionate, and butyrate, exert extensive and profound effects on proliferation, differentiation, and modulation of gene expression.[59] Of all the SCFAs, butyrate is a tumour-suppressive metabolite and a histone

deacetylase inhibitor, which has been considered to play a protective role in lymphomagenesis. A study conducted by Wei et al[60] demonstrated that butyrate could significantly inhibit the growth of lymphoma by providing a 3-level fibre diet and adding butyrate to the drinking water in different mouse tumour models. In parallel, the authors showed that butyrate could induce apoptosis of lymphoma tumour cells by triggering upregulated histone acetylation and the expression of several pro-apoptotic genes.

Dietary patterns modulate the composition and diversity of gut microbiome and further determine the end products of intestinal microbial flora metabolism.[61] Some of these microbial metabolites can promote or suppress carcinogenesis. For example, most of the SCFAs, produced by the fermentation of dietary fibre by 2 main bacteria phyla (*Bacteroidetes* for acetate and propionate; *Firmicutes* for butyrate), are generally considered as anticarcinogenic. However, tryptophan, one of the essential aromatic amino acid supply from nutritional sources, might contribute to the development of cancer.[57] Of note, it has been estimated that lymphoma incidence is associated with certain dietary components.[62-64] More specifically, there is an elevated risk of lymphoma with a high intake of red meat and animal fat; however, a greater consumption of fruits, soy, and green vegetables is linked with a decreased risk. Furthermore, in patients with diabetes mellitus type 2, an increased incidence of NHL was observed in a recent meta-analysis.[65] Interestingly, in an experiment with male mice,[66] the authors found that animals fed a restricted diet not only survived longer than controls but also showed a lower spontaneous lymphoma incidence. These results further imply a potential linkage between metabolism and lymphomagenesis, and the management of dietary patterns and microbial metabolites might be helpful in the treatment of patients with lymphoma.

Inordinate bacterial toxins related to genotoxicity

Genotoxicity is another carcinogenic mechanism linked with the microbiota capable of producing toxins, which can directly modulate tumorigenesis by inducing structural DNA damage.[31] Several bacterial toxins have been well demonstrated to play an essential role in various diseases, such as cytolethal distending toxin, colibactin, and enterotoxigenic *Bacteroides fragilis* in colorectal cancer,[67-69] as well as cytotoxic necrotizing factor 1 in prostate cancer.[70] Moreover, several bacterial-derived metabolites, such as hydrogen sulphide and reactive oxygen species, may lead to genomic instability.[71,72] Every time the intestinal barrier fails, these genotoxins are transferred or delivered to directly contact host cells to confer carcinogenic effects by affecting tumour suppressor genes or oncogenes.

Strikingly, genetic aberrations linked with the development of a vast subclass of lymphomas have been extensively reported.[73,74] These aberrations account for maladjusted activation of a wide cascade of signalling pathways and other cellular processes, such as those related to cell differentiation, cell receptor signalling, activation of the NF-κB pathway, apoptosis, and epigenetic regulation.[75] Importantly, in a study of an ataxia-telangiectasia mouse model,[76] the authors revealed that *Lactobacillus johnsonii* could reduce immune-mediated oxidative stress and systemic genotoxicity by decreasing NF-κB activation, which might decrease lymphoma penetrance.

Taken together, these mechanisms provide evidence for the intriguing notion that the gut microbiome, not mere bystanders but active participants, influences multiple facets of the genesis of lymphoid neoplasms. Although we discuss these putative mechanisms separately, they are likely to reciprocally interact with each other and work synergistically to expedite the pathogenic progress of lymphoma. Similarly, other unknown mechanisms are also possibly collectively engaged. Accordingly, we propose the microbiota-gut-lymphoma axis (Figure 1) for better knowledge of this microbiota-driven lymphoma field and further clinical translation. Nonetheless, research in this field is limited, and the causal relationships between the gut microbiome and lymphomagenesis are currently elusive. Therefore, attempts to identify the specific 'pro-lymphomagenesis' or 'anti-lymphomagenesis' microorganisms and explore the potential molecular mechanisms are urgently required.

Microbiota-Gut-Lymphoma Axis for Clinical Translation

Although current evidence on the interactions between the gut microbiome and a large fraction of lymphoma subtypes is relatively insufficient, the microbiota-gut-lymphoma axis indeed provides a promising treatment opportunity for patients with lymphomas.

Tools for diagnostic and clinical intervention in lymphoma

Auxiliary diagnosis. Accurate biomarkers are needed for detecting lymphoma, especially for patients at an early stage, in which a better clinical outcome can be achieved than that in patients presenting with advanced-stage disease.[3,4] Therefore, an accurate, affordable, and non-invasive test with high sensitivity for lymphoma is highly desirable. In addition to the paradigm that every diagnosis of gastric MALT lymphoma should prompt a thorough investigation for *H pylori*,[47] the presence of faecal microbial dysbiosis in patients with ALL and possible biomarkers of the gut microbiota profiles for identifying patients from control groups at the time of disease diagnosis have been reported.[27,29] Although more studies are warranted, these data reveal the potential for developing novel diagnostic strategies based on stool.

Clinical intervention. To date, gastric MALT lymphoma is the only malignancy for which antibiotics are the first choice of

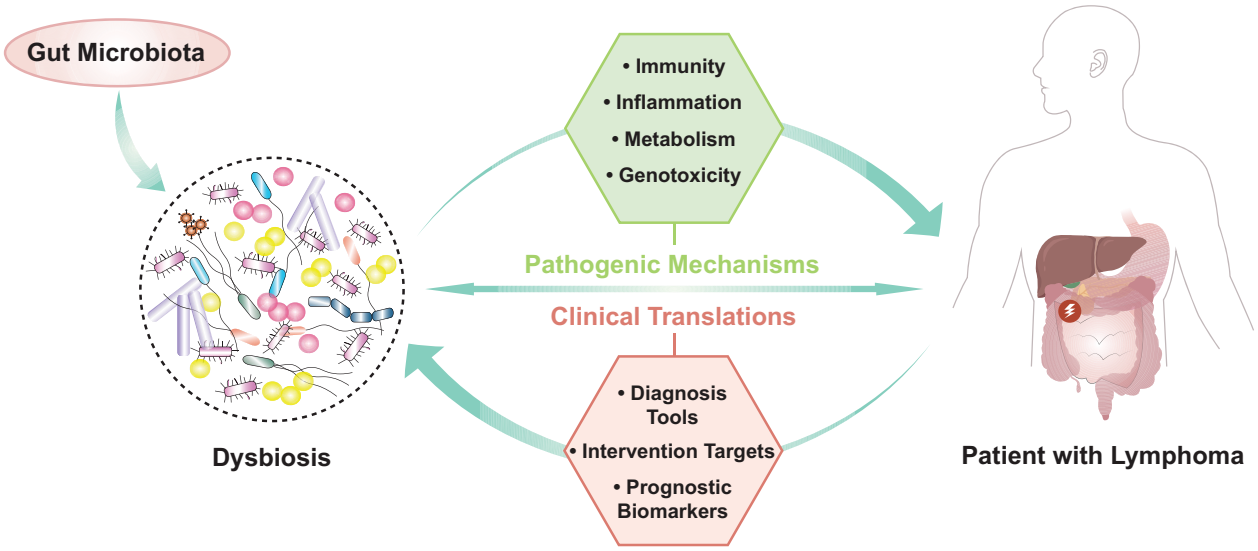

Figure 1. Microbiota-gut-lymphoma axis. Immunity, inflammation, metabolism, and genotoxicity are the 4 most likely postulated molecular mechanisms involved in lymphomagenesis, which provide a promising treatment opportunity for patients with lymphoid neoplasms, such as gut microbiota tests as screening tools and prognostic or predictive biomarkers, as well as modulating microorganisms to prevent, treat, and reduce treatment-related adverse effects.

therapy with curative intent, and the oral recombinant vaccine targeting *H pylori* exhibits efficacy and safety to substantially reduce the incidence of *H pylori* infection.[77] Interestingly, in a prospective study based on 16S rRNA sequencing,[78] the researchers revealed that *H pylori* infection induces gastric microbial dysbiosis involved in gastric carcinogenesis, and the microbial diversity and community structure can be restored to a similar status of negative individuals by successful eradication. Therefore, it will be helpful for prevention strategy to investigate the changes in gastric microbiota in gastric MALT lymphoma before and after anti–*H pylori* therapy. Furthermore, faecal microbiota transplantation (FMT) has been investigated as a treatment option in a variety of diseases, and recurrent *Clostridioides difficile* infections can be cost-effectively cured.[79,80] Several studies have suggested that FMT may be a promising regimen for recurrent *C difficile* infections in patients with lymphoma enduring haematopoietic stem cell transplantation (HSCT).[81-83] However, it is noteworthy that patients with lymphomas are in an immune disorder status, and these patients are more predisposed to FMT-related adverse effects, such as infection, when applying FMT improperly. Even so, FMT might be attractive for the treatment of comorbidities in patients with lymphoma, and modulating the gut microbiota is a promising tool for lymphoma therapy and prevention.

Biomarkers for treatment-associated adverse effects in patients with lymphoma

Chemotherapy. Associations of the gut microbiota with chemotherapy response and toxicity have been widely recognized.[84,85] Although much progress has been made in the treatment of lymphoma, chemotherapeutic agents remain a major staple, whereas their use is always linked with significant toxicity.

A few studies have indicated that intensive chemotherapy has a notable effect on the gut microbiota in patients with lymphomas (Table 2),[27,86-88] which significantly reduces microbial diversity. Hakim et al[87] conducted an investigation of the microbial features of faecal samples from 199 children with newly diagnosed ALL, and the authors found that the relative abundance of certain bacterial taxa could predict the development of chemotherapy-related adverse effects, such as *Enterococcaceae* or *Streptococcaceae* with infections, as well as *Proteobacteria* with febrile neutropenia. However, the contribution of chemotherapy to the variation in the gut microbiota remains to be elucidated due to confounding factors, such as antibiotics.

Allogeneic HSCT. Allogeneic HSCT is used as a curative treatment for various haematologic diseases, including malignancies, but it can be accompanied by severe side effects, such as infections, acute graft-versus-host disease, and death.[89] Of note, perturbations in the gut microbiota during allogeneic HSCT characterized by loss of diversity and domination by a single taxon have been well profiled in a multicentre prospective longitudinal cohort study,[90] and an increasing number of studies have begun to pay attention to connections between the intestinal microbiota and HSCT-associated adverse effects.[91] A study using machine learning that included 28 patients with NHL undergoing allogeneic HSCT established a bloodstream infection risk index that could predict the future risk of bloodstream infection in these patients with a sensitivity of 90% at a specificity of 90% based merely on the pretreatment of faecal microbiome.[92] Moreover, correlations between the gut microbiota and graft-versus-host disease as well as pulmonary complications in patients suffering from HSCT have been identified.[93,94]

Table 2. Major human studies on the effect of chemotherapy on the gut microbiota of lymphoid neoplasms by high-throughput sequencing.

STUDIES	INDIVIDUALS (CASE VS CONTROL, N)	SAMPLE TYPES	AMPLIFIED REGIONS	PRIMARY FINDINGS
Rajagopala et al[27]	28 paediatric and adolescent patients with ALL vs 23 matched healthy siblings	Faecal samples	V1-V3	Microbiota diversity changes during chemotherapy and maintenance therapy
Montassier et al[86]	28 patients with non-Hodgkin lymphoma before vs after chemotherapy	Faecal samples	V5-V6	Significant decreases in the abundances of *Firmicutes* and *Actinobacteria* and significant increases in the abundance of *Proteobacteria* following chemotherapy
Hakim et al[87]	199 patients with ALL before vs after phase I of chemotherapy	Faecal samples	V1-V3	Significant decreases in the microbial diversity and the relative abundance of *Bacteroidetes* and significant increases in the abundances of *Clostridiaceae* and *Streptococcaceae* after chemotherapy
Nearing et al[88]	16 paediatric patients with ALL in the first 6 months of therapy	Faecal samples	V4-V5 and metagenomic shotgun sequencing	Multiple significant differences in both taxonomic and functional profiles between samples from patients with and without infectious complications within the first 6 months of therapy

ALL: acute lymphoblastic leukaemia.

Immunotherapy. Immunotherapy is broadly used to treat an array of malignancies and has revolutionized the therapeutic modality of cancer.[95] Immune checkpoint blockade therapy (CBT) stands at the forefront of immunotherapy, which has demonstrated remarkable effectiveness with an acceptable safety profile in specific lymphoma subtypes, such as classical HL[96] and primary mediastinal B-cell lymphoma,[97] which both have recently been considered 'inflamed lymphomas' based on their immune landscapes.[98] Furthermore, growing evidence highlights that the gut microbial composition has a major influence on the effectiveness of anticancer immunosurveillance and might have a determinant role in invigorating CBT.[99]

It has been demonstrated that not only can the gut microbiota help to stratify patients receiving CBT in responders and non-responders but also the efficacy of CBT and resultant clinical outcomes are truly determined by the dominance of certain microbes.[100,101] Converging findings have indicated that the response of CBT in several malignancies diminishes with prior administration of antibiotics by inducing gut microbial dysbiosis,[102-104] whereas several bacterial species that are favourable for anticancer immunosurveillance, including *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, and *Bifidobacterium* spp, have been identified.[99] Thus, it might be possible to manipulate the gut microbiome towards a status that promotes immune-mediated tumour control. Moreover, a recent study proposed the potential of the gut microbiome to enhance the responses of chimaeric antigen receptor T-cell therapy, which is another remarkable advance in cancer immunotherapy.[105]

Associations of Microorganisms Beyond the GIT with Lymphoma

Given that lymphoma can originate in and involve every organ in the body, alterations of the microbes in other non-intestinal contexts, such as the skin, conjunctiva, and oral cavity, are also amenable to contribute to the genesis of several lymphoma subtypes, for instance, a higher colonization rate of *Staphylococcus aureus* in the skin of cutaneous T-cell lymphoma,[106] *Chlamydia psittaci* in ocular adnexa MALT lymphomas,[107] and *Borrelia burgdorferi* in cutaneous B-cell lymphoma.[108] A recent study based on 16S rRNA and whole-genome shotgun sequencing revealed a relative reduction in a suite of opportunistic pathogens in active mycosis fungoides skin lesions compared with that in contralateral healthy-looking skin.[109] Moreover, increased early oral exposure to the microbiome conveys a protective role for young adult HL,[110] and maladjusted microbiota of the oral cavity and conjunctiva have been reported in cases with paediatric ALL and conjunctival MALT lymphoma, respectively.[111,112] While the mechanistic role is undefined, these data highlight that the commensal microbiome outside the GIT may play a role in malignant lymphocyte transformation and consequently may serve as a therapeutic target.

Landscapes of Diverse Viruses in Lymphoma

Multiple viruses closely interact with lymphomagenesis, such as *human T-lymphotropic virus type I* with adult T-cell leukaemia-lymphoma,[113] *HIV virus* with AIDS-defining lymphoma,[114] and *hepatitis B virus* and *hepatitis C virus* with NHL.[115,116] Most notably, *Epstein-Barr virus* (EBV), the first discovered human tumour virus, is intimately implicated in the genesis of several lymphoma subtypes, and the EBV genome has been subsequently detected in Burkitt lymphoma, post-transplant lymphoproliferative disease, HL, and natural killer/T-cell lymphoma.[117]

Integrating microbial DNA into the host genome is a widely accepted virulence mechanism of viruses for invasive human tumours, which is also known as genomic integration.[31] Note that this carcinogenic effect depends on the transcription

of viral proteins; for example, EBV can encode several latent proteins crucial for the transformation of B lymphocytes into virally immortalized B cells,[118-121] and the causal links between the diverse group of viruses and corresponding malignancies have been reviewed elsewhere.[122] Intriguingly, one study demonstrated that *herpesvirus* latency confers symbiotic protection from bacterial infection.[123] Thus, microbial dysbiosis might be a consequence of alterations in the virome. In addition, certain protozoa, for example, *malaria*, can increase the risk of endemic Burkitt lymphoma by interacting with EBV-infected B cells.[124] However, the impacts of non-bacterial microorganisms on carcinogenesis have been substantially underestimated, as most studies focus merely on intestinal bacteria.

Limitations and Future Perspectives

Overwhelming evidence from the past decades supports a key contribution of the gut microbiota to multiple diseases. Culture-independent technologies to study microbial communities have significantly advanced our knowledge of the human gut microbiome. To date, however, only relatively limited data feature the role of the gut microbiota in lymphomas, which is somewhat surprising given their intimate relationships. There are for inherent restrictions, such as large diverse ethnic origins, dietary habits, and the lack of standardized sampling protocols and statistical correction among studies. Other crucial limiting factors are summarized as follows. First, lymphoma is a highly heterogeneous malignancy with various subtypes and diversified non-specific clinical manifestations (eg, painless lymphadenopathy, fevers, drenching night sweats, and weight loss),[4] and as a result, timely and accurate diagnosis is often difficult. In addition, antibiotics or other antipyretic drugs, even glucocorticoids, are frequently used whenever fever of unknown origin is difficult to manage, which affects the composition of the gut microbiome so saliently as to impair further causal relationship explorations. Finally, microbiota-driven signal regulation pathways implicated in the pathogenesis of lymphomas are far from unambiguous, and establishing stable animal models is also a substantial challenge.[125]

Overall, the gut microbiome and the genesis of lymphoma are highly contextual, and the microbiota-gut-lymphoma axis provides a fascinating avenue for clinical translation. However, as many considerations are based on observational studies, a plethora of questions remain largely unexplained and warrant investigation. First, attempts must be undertaken to appreciate the intestinal microbial shifts in an assortment of patients with lymphoma in well-designed studies. In addition, further functional studies combining omics technologies (eg, metagenomics, metabolomics, metatranscriptomics, and metaproteomics) are imperative to evaluate the causal relationships between the gut microbiome and lymphomagenesis and the underlying mechanisms. Finally, the clinical implications of the gut microbiota as a novel biomarker or target for the clinical management of patients with lymphoma must be validated in prospective cohorts. Similarly, interactions of microbial floras beyond the GIT with the microbiota-gut-lymphoma axis merit further study.

Conclusion

In summary, as the largest assembly of microorganisms, the gut microbiota is likely to play a leading role in the development of lymphoma, and the microbiota-gut-lymphoma axis presents a promising target for preventive approaches. Although challenging, future elucidation of the complex mechanisms of microbiota-mediated lymphomagenesis will be integral to allow the advancement of future personalized therapeutic strategies for cancer care.

Author Contributions

M.Z. and Z.S. designed the study. Z.S. collected data and wrote the manuscript. Both authors have read and agreed to the published version of the manuscript.

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