

The human microbiome in hematologic malignancies

Abstract

The significant role of gut microbiome in human physiology, immune modification and nutrients supply has been recognized and is advancing. Scientific reports suggest association of the human microbiome with the risk of various diseases including hematologic malignancies. Metabolites (such as short chain fatty acids (SCFAs)) released into the gut as a result of bacterial fermentation can enter the circulation and change the systemic metabolome. This can influence hematopoiesis and the nature of cells recruited to sites of inflammation. Bacterial metabolites especially SCFAs have an important role in host metabolism and serve to modulate immune responses. They have potential to activate several G protein-coupled receptors (GPCRs) expressed on various immune cells. SCFAs have been shown to suppress nuclear factor Kappa B (NF- κ B) and inflammatory cytokines like IL-6 and tumor necrosis factor α (TNF- α) and they can also induce IL-10 production consequently affecting the generation of Th1 and Th17 cells and drive proliferation of T cells and B cells. The intimate, bidirectional relationship between microbes and host immune responses suggests the association of the microbiome with lymphoma and blood cancer. The role of pathogenic organisms such as *Borrelia burgdorferi*, *Chlamydia pneumoniae*, Epstein-Barr virus (EBV), hepatitis C virus (HCV), *Helicobacter pylori* and *human immunodeficiency virus* (HIV) has been suggested to be associated with hematologic malignancies. Changes in the microbiome can result in excessive infection, tissue damage and pathology as well as in the development of hematologic malignancies and subsequently can have direct impact on overall patient outcome.

Keywords: hematopoiesis, bacteroidetes, lymphoma, *helicobacter pylori*, *mycobacterium tuberculosis*

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Abbreviations: SCFAs, short chain fatty acids; HM, human microbiome; GIT, gastrointestinal tract; MAMPS, microorganism-associated molecular patterns; GPCRs, G protein-coupled receptors; NF- κ B, nuclear factor kappa B; TNF- α , tumor necrosis factor- α ; EBV, Epstein Barr virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PTLN, post transplantation lymphoproliferative disorder; CS, cesarean section; ALL, acute lymphoblastic leukemia; MALT, mucosa associated lymphoid tissue; AT, ataxia telangiectasia

Introduction

Accumulating research-based evidence has drawn our increased awareness towards the relevance of the Human Microbiome (HM) towards healthy and homeostatic human physiology. Various areas on and within the human body, including conjunctiva, respiratory tract, oral and otic cavities, surface of skin, urogenital tract and the Gastrointestinal Tract (GIT) serve as ecosystems for microbial communities comprising the human microbiota.¹ As a modulation resulted from evolution, humans harbor about 10^{14} microorganisms consisting of at least 1000 distinct microbial species, outnumbering human somatic cells by about 10 to 1.^{2,3} The total HM encodes about 4×10^6 genes versus the $\sim 26,600$ genes of the human host, thus outnumbering host genes in the order of about 150 to 1.⁴ The mammalian GI tract is mainly composed of bacteria but also contains fungi, archaea and viruses. It is dominated by anaerobic *Firmicutes* ($\sim 51\%$) and *Bacteroidetes* ($\sim 48\%$). The remaining 1% is consisting of *Proteobacteria*, *Verrucomicrobia*, *Fusobacteria*, *Cyanobacteria*, *Actinobacteria* and *Spirochetes*, including various species of fungi, protozoa, viruses and other microorganisms.⁵ This one percent of the microbiome is considered relevant, as they may contribute to disease if their proliferation is not under control resulting in dysbiosis.^{2,6,7}

The microbiota encompass a wide variety of microorganisms (bacteria, viruses, protozoa, fungi and archaea) and this eclectic ecosystem shares the body space of every individual, creating a commensal, symbiotic and pathobiont relationship that has garnered increasing attention regarding its role in carcinogenesis.⁸ Of all body surfaces, the gastrointestinal tract harbors the greatest number and diversity of microbes in the human body, with bacteria representing the bulk of the microbiota (10^{12} bacteria/gm feces).^{9,10}

The effects of microbiome on inflammation and carcinogenesis are likely to be organ specific as the microbiome of each organ is distinct. There is an important and functionally relevant inter-individual variability of the microbiome composition carrying a potential determinant of disease (including cancer) development. In addition, microbial community and abundance vary in different locations within organs. Many organs such as liver, which are without their own microbiome niche, may be exposed to microorganism-associated molecular patterns (MAMPs) and bacterial metabolites through anatomical links with the gut.¹¹ The intestinal microbiota and the respiratory microbiota are linked to each other to some extent, possibly by micro aspiration of swallowed particles or in the opposite direction by coughing, mucociliary clearance and swallowing.^{12,13}

Microbiome, immune response and hematologic malignancies

SCFAs having an important role in host metabolism also serve to modulate immune responses. They can activate several G Protein-Coupled receptors (GPCRs), such as GPR43, which is expressed by granulocytes and by other myeloid cells¹⁴ or such as GPR109a, a receptor for niacin and C4 expressed by gut epithelial cells, adipocytes, macrophages and dendritic cells. Their signaling through GPCRs suggests their wide spread functions in host immune

response. SCFAs have been shown to suppress Nuclear Factor Kappa B (NF- κ B) and inflammatory cytokines like IL-6 and Tumor Necrosis Factor α (TNF- α) and they can also induce IL-10 production.^{15,16} These cytokines have potential to further affect the generation of Th1 and Th17 cells and drive proliferation of T cells and B cells.¹⁷ Bacterial byproducts such as SCFA of the gut microbiome can also impact allergic airway disease by interacting with cells of the bone marrow compartment after entering the systemic circulation.¹⁸ Butyrate, a type of SCFA, has potential to enhance T-cell apoptosis and decreases accumulation of T cells in inflamed colonic mucosa by up regulating Fas.¹⁹ Polysaccharide A, a carbohydrate produced by the human commensal bacterium *Bacteroides fragilis*, is sufficient to ameliorate T cell-driven colitis in an IL-10-dependent manner.²⁰ Further, germ-free mice have an immature mucosal immune system,²¹ so collectively these findings support the major and important role of host microbiome in immune responses and immune disorders correspondingly.

Studies have suggested tumor-promoting effects as well as antitumor effects of the bacterial microbiota.¹¹ The significant role of gut microbiome in human physiology, immune modification and nutrients supply has been recognized and is advancing. Scientific reports suggest human microbiome association with the risk of gastric, oesophageal, hepatobiliary, pancreatic, lung, colorectal and other cancers. There are indications of microbial associations with a few other cancer sites like neck, throat and breast cancers as well.²² Specific components of human microbiome like *Helicobacter pylori*, *Salmonella typhi*, *Neisseria elongata* and *Streptococcus mitis*, *Campylobacter jejuni*, *Mycobacterium tuberculosis* and dysbiosis of *Fusobacterium* and *Porphyromonas* have been specifically linked with specific human cancers. Although, the microbiome has not yet been studied comprehensively in these cases, the intimate, bidirectional relationship between microbes and host immune responses suggests the association of the microbiome with lymphoma and blood cancer. The seropositivity to *Borrelia burgdorferi* was associated with cutaneous B-cell non-Hodgkin lymphoma in one of two studies in Scandinavia.^{23,24} *Chlamydomphila psittaci* has been detected in Mucosa-Associated Lymphoid Tissue (MALT) lymphomas in various non-gastrointestinal organs.²⁵ Increase in circulating platelet count can be secondary to increased serum interleukin levels (especially IL-6) and its production is induced by inflammatory process like bacterial infection or sepsis. This might be associated with malignant thrombocytemic conditions however yet need to be investigated.²⁶ It is reported that the Post Transplantation Lymphoproliferative Disorder (PTLD) after solid organ transplant and HCT is associated with Epstein-Barr virus (EBV), which leads to uncontrolled B-cell proliferation and tumor formation.²⁷

The metabolites (such as SCFAs) released into the gut as a result of bacterial fermentation can enter the circulation and change the systemic metabolome. This can influence hematopoiesis and consequently the nature of cells recruited to sites of inflammation.^{12,28} In an analysis of host microbiome related effects on the risk for lymphoma, and whether changing the bacteria can reduce this risk. Yamamoto ML et al.²⁹ reported that mice with Ataxia-Telangiectasia (A-T), a genetic disease that in humans and mice is associated with a high rate of B-cell lymphoma. They discovered that of mice with A-T, those with certain microbial species lived much longer than those with other bacteria before developing lymphoma, along with less gene damage (genotoxicity).²⁹ The role of other pathogenic organisms such as EBV, hepatitis C virus (HCV), *Helicobacter pylori*

and *human immunodeficiency virus* (HIV) in lymphomagenesis has been reported as well.³⁰ The mode of delivery serves as primary exposure to the maternal microbiome and thus plays an important role in establishing the core human microbiome. Cesarean section (CS) delivery is proposed as modulator of both immune response and early-life infection which have been suspected in the etiology of childhood leukemia, specifically acute lymphoblastic leukemia (ALL).³¹

Conclusion

The microbiome has become the focus of active research over the last few years. Nowadays it is understood, that the microbiome presents a critical factor in innate and adaptive immune responses and in pathophysiology of associated diseases. Its effects go beyond just colonization and infection, but modulate distinct signaling pathways and drive certain phenotypes of disease. Changes in the microbiome can result in excessive infection, tissue damage and pathology and subsequently can have direct impact on overall patient outcome. Of importance, the microbiome seems to be directly involved in the development of hematologic malignancies. While this is a new challenge for clinical physicians from a knowledge perspective, at the same time it opens up opportunities for a more personalized medicine approach by modulating the microbiome before and during disease course.

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Conflict of interest

The author declares no conflict of interest.

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