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Review Article

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Microbiota and Hematological Diseases

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ABSTRACT

The microbiota is directly involved in the host metabolic process, as well as in immune response modulation and recruitment of different cells typology in the inflammatory site. Human microbiota modification (dysbiosis) is a condition which could be correlated with various pathologies. The short-chain fatty acids produced by the metabolic process have an important role as immune mediators. In hematology field, dysbiosis can represent a predisposing condition for triggering and/or conditioning both non-neoplastic (iron deficiency anemia, thrombosis, thrombocytosis or thrombocytopenia) and neoplastic disorders (lymphomas, leukemias, myeloma). Dysbiosis may also interfere on therapy efficacy (iron supplementation, chemotherapy, immunotherapy, and hematopoietic stem cell transplantation), impacting on patient's outcome.

Keywords: Microbiota; Anemia; Thrombosis; Leukemia; Lymphoma; Multiple Myeloma

INTRODUCTION

The microbiota represents the most conspicuous part of micro-organisms present in the human body. Microbiota composition is estimated to be more than 10 times the total number of human cells and it resides principally (99%) in gastrointestinal tract, colon and small intestine [1,2]. The microbiota changes more or less significantly and rapidly; genetic factors, antibiotic therapy, immune response and occasional infections influence microbiota composition.

Functionally, the microbiota is involved principally on maturation, regulation and modulation of immune system, as well as on vitamins (folic acid, vitamin K and group B vitamins), and amino acids production.

The terms microbiota and microbiome are often interchangeable. The microbiome is the set of micro-organisms found in the specific environment (bacteria, viruses and fungi); the microbiota is the set of genomes of all micro-organisms present in the environment.

About 60% - 70% of bacteria located in the human intestinal tract cannot currently be cultured with the available methods[3]. DNA sequencing technologies (metagenomics) investigates both the genes expressed by microbiota and the interactions between bacteria and multicellular organisms. By 16S rRNA genomic sequencing we can identify a single bacterial species; moreover, microbiome gene study identifies molecules that autonomously are not synthesized [4, 5].

The microbiota plays an important metabolic role producing short-chain fatty acids (SCFAs), as well as the increase in proteolytic activity. The SCFAs have an important role as metabolic and immune mediators; in elderly people their decrease favors

the intestinal age-related inflammation process[6, 7]. The interaction between commensal microbiota and immune system is crucial for a proper immune function [8]. Microbiota transitional change from eubiosis to dysbiosis condition can increase the incidence of cardiovascular, inflammatory, neurological, psychological, oncological and metabolic pathologies[9,10] (Figure 1).

Microbiota and hematopoiesis

The normal hematopoiesis process is regulated by growth factors and cytokines that act as extrinsic regulators, while the epigenetic and transcriptional factors act on the hematopoiesis as intrinsic regulators. The two regulatory processes, normally, allow the hematopoietic stem cells (HSC) differentiation towards hematopoietic progenitor cells (HPC), up to the mature circulating cells (Figure 2). The microbiota, through the Stat1 signal, can affect hematopoiesis.

In the context of hematopoietic process, the microbiota can play a role in hematological and onco-hematological pathologies. The intestinal microbiome imbalance, dysbiosis, can promote the suppression of hematopoiesis. In inflammatory bowel diseases (IBD), which are characterized by commensal intestinal bacteria imbalance, a condition of non-drug dependent aplastic anemia can occur[11,12]. Table 1 reports the correlation between microbiota and some of the most frequent onco-hematologic pathologies, specifying the microbial populations involved or suspected and their mechanisms [13].

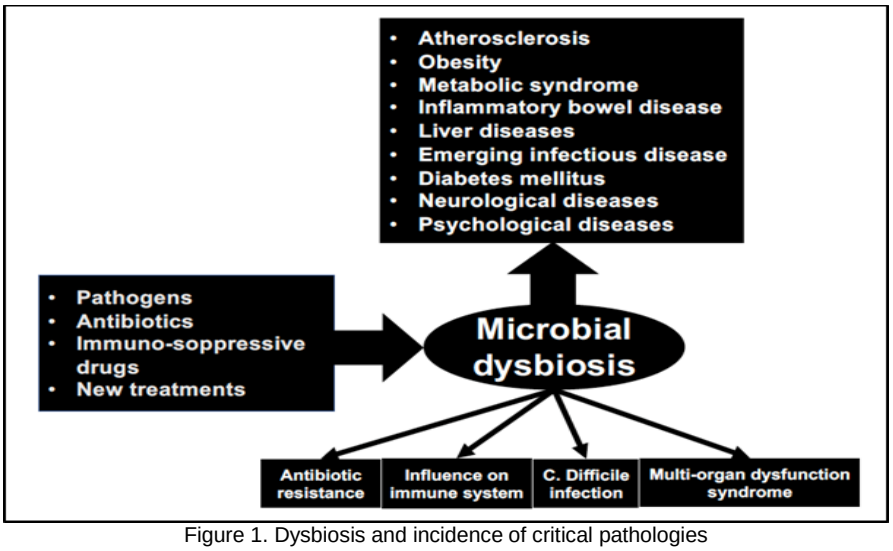

Figure 1. Dysbiosis and incidence of critical pathologies

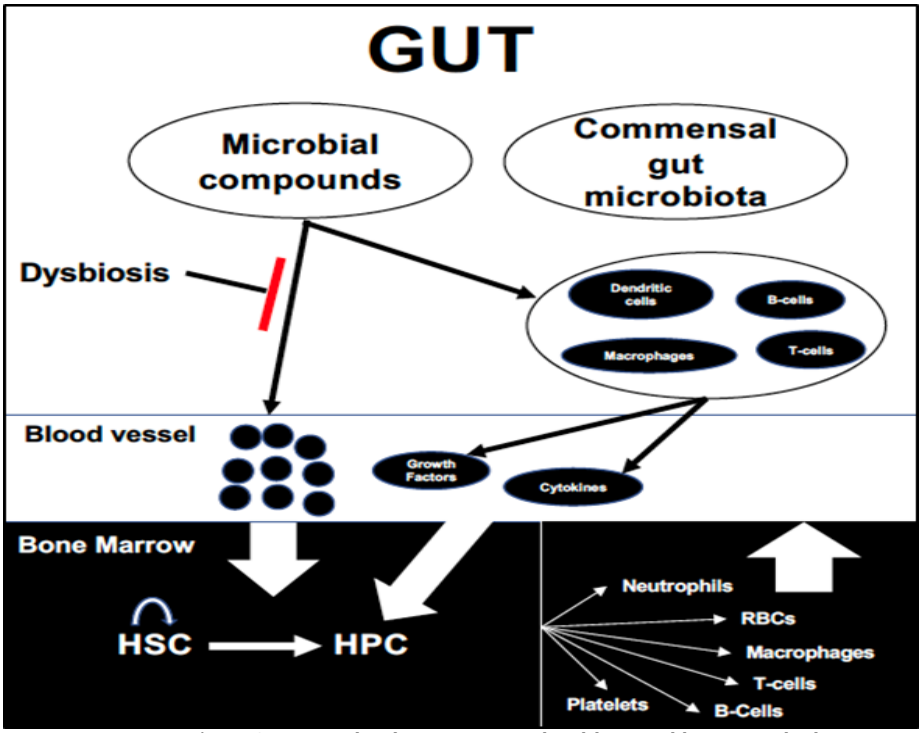

Figure 2. **Interaction between gut microbiota and hematopoiesis**
(HSC = Hematopoietic Stem Cell; HPC = Hematopoietic Progenitor Cell)

Table 1: Onco-hematological diseases and microbiota correlation. Main microbes involved or suspected and their possible pathogenetic mechanism

Onco-hematologic disease	Microbe involved or suspected	Mechanism
Acute lymphoblastic leukemia	Prevotella, Bacteroides Roseburia, Ruminococcus 2, Anaerostipes, Coprococcuss, Faecalibacterium, Aerococcaceae and Carnobacteriaceae, Firmicutes, Lactobacillales, Abiotrophia, Granulicatella, Bacilli	Immune system dysregulation through IL-6, HLA-DR+CD4+ and HLA-DR+CD8+ T cells
Hodgkin lymphoma	Gut microorganisms during childhood	Immunological alterations: < Th1 and > Th2, > IgE, < NK, < T-CD8+
Non-Hodgkin lymphoma	Helicobacter spp., gut microorganisms, Chlamidia psitacci, Campylobacter jejuni, Borrelia bergdorferi, Streptococcus bovis; HCV, HTLV-1	Abnormal DNA replication due to increase of B-ymphocyte growth Oxidative stress Oncogenic activation
Chronic lymphocytic leukemia	Anti-gram-positive antibiotics	Antagonism of antitumor activity of cisplatin [causes ROS-mediated-cell death] and cyclophosphamide [that activates T-helper antitumoral response]

Microbiota and anemia

Anemia is the most frequent symptom in patients with hemopathies, as well as in several non-hematological diseases that influence the hematopoiesis.

In anemia, the correlation between red blood cell production and microbiota is possible. In aplastic anemia there may be association with infections, such as viral hepatitis (e. g. A, B, C, E and G), *Cytomegalovirus* (CMV), *Epstein-Barr virus* (EBV) and *parvovirus B19* infections.

In anemia of chronic inflammation, supported also by bacteria, the cytokines production influences the hepcidin expression and, consequently, iron homeostasis alteration[14]. In some cases, infections due to specific types of bacteria can influence the hepcidin expression directly[15]. In both cases there may be a close correlation with microbiota alterations.

If bacterial infections can influence iron homeostasis, the opposite is also true. In fact, hemochromatosis[16] and chronic hemolytic anemias[17] can predispose the patients to bacterial infections.

Iron supplementation and microbiota

Iron is a vital element for most living organisms. It is essential not only for humans, but also for replication and survival of almost all bacteria, moreover, its "host-microbiota" relationship is direct.

In the proximal colon, the main iron transporter, divalent metal transporter 1 (DMT1), is located on the surface of the apical cells. This anatomical-functional localization is significant to increase the iron availability in the large intestine, which is rich in bacteria [18, 19].

When we give oral iron, expansion of specific enteric pathogens species can occur. Consequently, the beneficial proportion of microbiota can decrease and gastrointestinal inflammatory disorders can trigger. Moreover, oral iron can increase the production of reactive oxygen species (ROS); the oxidative stress activates the immune system in the host and cause inflammatory intestinal epithelial damage, a condition that predisposes to infection [20, 21, 22, 23, 24, 25].

Microbiota and platelets

Changes in both circulating platelet turnover and their concentration are uniquely influenced by microbial organisms during infections.

The association between *H. pylori* and immuno-thrombocytopenia (ITP) is known. Platelet activation occurs through *H. pylori* antibody FcγIIA, or through the interaction *H. pylori* bound von Willebrand factor (vWF) and platelet glycoprotein IB [26].

CMV and *varicella zoster* virus can also give thrombocytopenia. CMV directly infects platelets and triggers an ITP-like syndrome in immunocompromised patients[27]. Furthermore, in case of CMV infection there may be an important congenital platelet disorder, or the cytopenia may result from delayed platelet recovery after bone marrow transplantation.

In *Hepatitis-C virus* (HCV) infection the incidence of ITP is high and the pathophysiology is complex and multifactorial[28].

Patients with bacterial infection or sepsis show high levels of inflammatory cytokines, mainly IL-6, and subsequently an increase in circulating platelet count[29].

Microbiota and thrombosis

The direct correlation between coagulation and inflammation is known[30]. The intestinal bacterial flora can play a critical role in various inflammatory pathologies and trigger, directly or indirectly, a thrombotic condition (Figure 3).

The glycolipids (lipopolysaccharides) present on the outer membrane of gram-negative bacteria represent an important link between intestinal bacterial flora and hypercoagulability. Through this specific links, lipopolysaccharides activate both endothelial cells and platelets receptors and trigger the coagulation cascade[31].

The intestinal metabolization of certain foods produce metabolites, such as trimethylamine nitroxide (TMAO), which activate platelets and increase the possibility of cardiovascular diseases (CVD) (Figure 3). The administration of new choline analogues, modulate the intestinal bacterial flora and, consequently, the production of both lipopolysaccharades and TMAO. This could represent a new approach for atherothrombotic risk

reduction[32]. Since SCFAs regulate blood pressure, the altered conversion by intestinal microbiota from polysaccharades into SCFAs can cause problems on blood pressure regulation, increasing CVD risk.

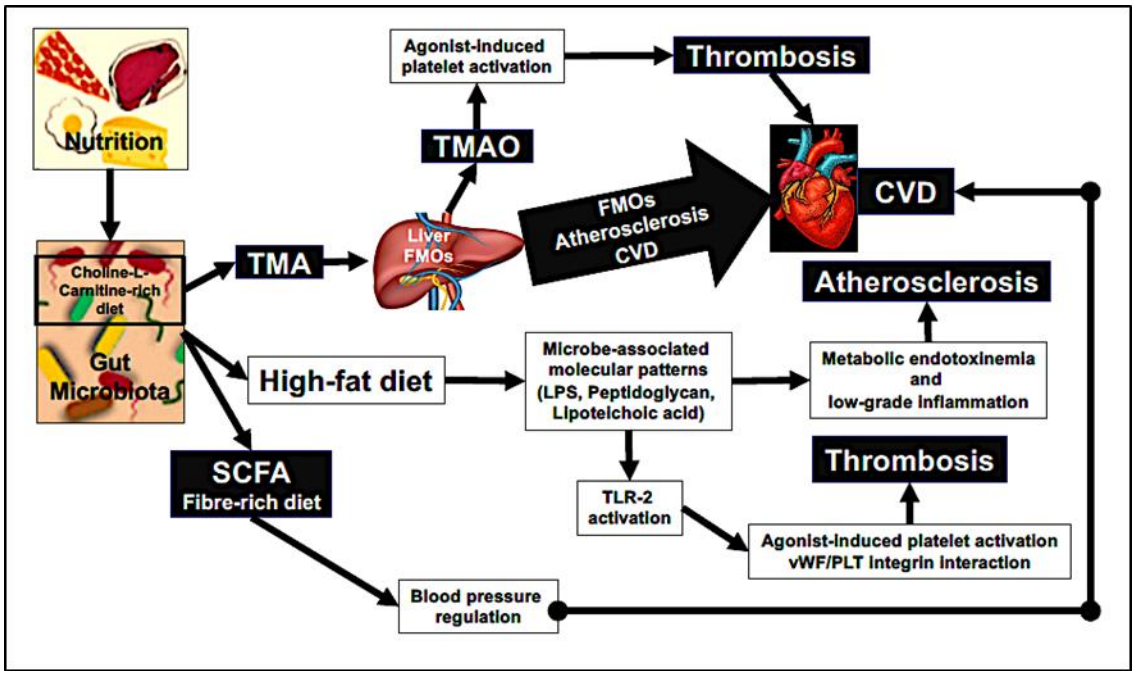

Figure 3. Nutrition, gut microbiota and risk of atherosclerosis, cardiovascular disease and thrombosis
TMA =Trimethylamine; TMAO = Trimethylamine nitroxide; FMOs = Flavin-monooxygenase enzymes; CVD = Cardiovascular disease; SCFA = Short Chain Fatty Acids; TLR = Tool Like Receptor; vWF = von Willebrand Factor; PLT = Platelets; LPS = Lipopolysaccharides

Microbiota and lymphomas

Dendritic cells and/or antigen-presenting cells (APC) constantly send signals to the immunologically active cells which belong to the mucosa-associated immune system. The immune response due to the intestinal microbial colonization causes the lymphocyte population to expand towards a tolerance or activation condition[33].

In *H. pylori* infection, the constant antigen presentation stimulation causes B-cell expansion[34,35]. MALT-lymphomas are associated with *H. pylori* infection in about 90% of cases[36,37], its eradication causes complete gastric lymphoma remission in about 80% of patients[38].

Beyond *H. pylori*, also *H. helmanii*, present in both humans and mice, can cause MALT-lymphoma and its presence has been detected in other chronic inflammatory conditions such as rheumatoid arthritis and colitis[39].

Cutaneous B-Cell non-Hodgkin lymphoma in *Borrelia burgdorferi* seropositivity have also been reported[40,41].

Microbiota and leukemia

Acute lymphoblastic leukemia (ALL) is the most common onco-hematological pathology in pediatrics. There may be a correlation with the onset of leukemia, according to the type of birth, at term or by cesarean section, when the newborn is exposed to vaginal bacteria [42]. The mutual influence between immune system and exposure to microbial

infections, both in utero and during childhood, in various studies are reported[43,44,45,46,47]. Furthermore, factors related to the microbiota colonization (breastfeeding and vaginal delivery) [48] or infections diagnosed before the diagnosis of leukemia, could affect the risk of childhood leukemia[49,50].

In newborns with ALL the high concentration of inflammatory markers is the evidence of a close correlation between immune system, expansion of B or T-cells and development of childhood leukemia[43].

Children in developing age, as well as children who are cancer survivors[51], in case of unhealthy eating habits (e. g. high fat intake, sodium, sweets and low fruit, vegetable intake) or on antibiotics therapy, show intestinal microbiota composition alteration, weight increase and possible onset or neoplasms restart [52, 53, 54, 55, 56, 57].

ALL adults in remission, generally, have problems several years after treatment. In those cases, the anal microbiota can change (dysbiosis) showing a reduced microbial diversity (increase *Actinobacteria*, decrease *Faecalibacterium*), and consequent immune alteration (altered levels of C reactive protein, IL-6, CD4+ and CD8+ T- cell) [58].

In acute myeloid leukemia (AML) the most isolated microorganism is the *Heterogeneous Viridans streptococci*, a gram-positive cocci [59].

An important specific action on leukocytes is showed by the interaction with leukotoxin A (LtxA) which is generated by the oral *Aggregatibacter actinomycetem comitans bacterium*. In patients with AML, the LtxA protein both *in vivo* and *in vitro* eliminate leukemic cells, while cells from healthy subjects are resistant to LtxA mediated cytotoxicity[60].

Within the hematopoietic differentiation process, an important function is supported by the exotoxin Panton-Valentine-Leukocidin (PVL) secreted by the *Staphylococcal synergohymenotropic*. It causes the lysis of the human polymorph nucleated, monocytes and macrophages and induces leukemic cells differentiation [61, 62, 63].

In Chronic Lymphocytic Leukemia (CLL) patients on concomitant antineoplastic and anti-gram-positive antibiotic therapy, they may show reduction in progression-free survival (PFS) and overall survival (OS) in case of significant intestinal dysbiosis [64].

In the context of extracolonic neoplastic pathologies, the association between *Streptococcus bovis* with chronic myeloid leukemia (CML) and CLL has also been described [65].

Microbiota and Multiple Myeloma

The plasma cell subclones expansion that characterize the progression of Monoclonal Gammopathy of Undetermined Significance (MGUS) towards Multiple Myeloma (MM) can be triggered by interaction between neoplastic plasma cells genetic changes and immune microenvironment[66]. A preclinical study has shown that *Prevotella heparinolytica* promote Th17 cells differentiation[67]. Th17 cells, which colonize the intestine, migrate towards the bone marrow favoring progression in MM. In Vk*MYC mice, either the lack of microbiome alteration or IL-17 deficiency delay progression in MM. High levels of IL-17 in bone marrow accelerate the progression of Smoldering Multiple Myeloma (SMM) towards MM. In addition, IL-17 induces plasma cell STAT3 phosphorylation and activates eosinophils. Blocking IL-17, IL-17RA and IL-5 through antibodies, both Th17 and eosinophils accumulation in bone marrow is reduced; consequently, the evolution towards an open MM is delayed. Probably, abnormal paracrine signals emission between adaptive and innate immunity through commensal bacteria accelerates the progression towards MM. The development of these studies may address towards the use of further targeted therapies.

Microbiota and hematopoietic stem cell transplantation

In allogeneic hematopoietic stem cell transplantation (aHSCT) the graft *vs* host disease (GvHD) morbidity is high (30% - 70%), with systemic and local complications [68]. GvHD involves organs in which there is a specific microbiota/epithelium interaction such as intestine, mouth and skin, eyes and lung, or the liver, in the latter the contiguity with the microbiome is ensured by the portal circulation. The microbiota/epithelium barrier integrity, in particular the intestinal one, plays an important role both in the immune homeostasis and GvHD trigger[69].

The intestinal epithelium damage, as well as the mucus integrity that covers it, exposes bacteria, bacterial products (lipopolysaccharide) and epithelial cells degeneration products to the antigen-presenting cells (APC). The consequent activation of alloreactive T cells donor causes an inflammatory condition with release of cytokines and damage of target organs.

Studies have highlighted the correlation between *Blautia* microorganisms and changes in microbiota structure, onset of GvHD and improvement of transplanted cells engraftment[70].

To limit the onset of GvHD it may also be appropriate to restore the intestinal microbiome diversity with the aim of increasing engraftment after transplantation. Probiotic microorganisms can modify the intestinal microflora and mediate anti-inflammatory activity The probiotic microorganism *Lactobacillus rhamnosus GG* would improve acute GvHD [71,72]. Restoration of microbiome diversity in patients undergoing aHSCT have been carried out by normal fecal microbiome transplanting (FMT); the outcomes in some cases appear to be promising [73].

Microbiota and chemotherapy

Chemotherapy (CHT) generally causes major gastrointestinal problems and, significantly, immunosuppression with febrile infection and bloodstream infection. The resulting antibiotic therapy causes microbiome alteration and dysbiosis. Bacterial species reduction in microbiome can influence the antitumor effect of some drugs and the possible anti-tumor drug effect[74] Doxorubicin antitumor action can be decreased by *E. coli* and *Parabacteriodes distasonis*[75], as well as the *Lactobascillus acidophilus* which can reduce the cispatin activity[74]. A modulating action on 5-FU activity is possible through the bacterial production of Vit. B6 and Vit. B9[75]. A critical role on cyclophosphamide antitumor activity can be played by *Barnesiella intestinihominis* and *Enterococcus hirae*, in fact their removal causes resistance to cyclophosphamide [75]. *Fusobacterium nucleatum*, by selective loss of miR-18a* and miR-4802 via TLR4 and MYD88, triggers an autophagic process as well as chemoresistance [75].

Microbiota and immunotherapy

Even in case of immunotherapy the intestinal microbiome can modify the tumor response 75, 76. Treatment response and tumor immunity improvement could depend by bacteria type, as well as the intestinal microbiome diversity [77].

In patients with melanoma and responsive to anti-PD1 therapy, the analysis of fecal samples found a high presence of bacteria belonging to the *Ruminococcaceae* family [78]. Patients with advanced melanoma and resistant to immune checkpoint inhibitor therapy, can show a significant response to therapy after FMT. In these cases, FMT determines both immune and therapeutic response with a significant recognition and killing of neoplastic cells[79].

CONCLUSION

The aim of this review is to report the main interactions between microbiota and both hematological and onco-hematological diseases. In hematological clinical studies the prognostic and therapeutic aspects related to the microbiome variations not always are systematically reported. Generally, this possible particular correlation is referred as case reports, and the number of patients often is limited. Furthermore, the microbiome study must be carried out and validated in specialized laboratories.

The microbiome analysis, for its: i) genetic diversity, ii) important immune activity, iii) ability to influence the metabolism and modulate drug interactions, could allow us to understand the correlation between intestinal microflora changes and trigger or modify multidisciplinary pathologies, not only in hematologic field.

CONFLICT OF INTEREST

The author has no potential conflicts of interest.

REFERENCES

1. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016; 14(8): e1002533.
2. Sommer F, Bäckhed F. The gut microbiota–masters of host development and physiology. Nat Rev Microbiol. 2013; 11(4): 227 - 38.
3. Suau A, Bonnet R, Sutren M, et al. Direct analysis of genes encoding 16S rRNA from complex communities reveals many novel molecular species within the human gut. Appl Environ Microbiol. 1999; 65(11): 4799 - 807.
4. Weisburg WG, Barns SM, Pelletier DA, et al. 16S ribosomal DNA amplification for phylogenetic study. J Bacteriol. 1991;173(2): 697 - 703.
5. Amann R, Springer N, Ludwig W, et al. Identification in situ and phylogeny of uncultured bacterial endosymbionts. Nature. 1991;351(6322): 161- 4.
6. Woodmansey EJ, McMurdo MET, Macfarlane GT, et al. Comparison of compositions and metabolic activities of fecal microbiotas in young adults and in antibiotic-treated and non-antibiotic-treated elderly subjects. Appl Environ Microbiol. 2004; 70(10): 6113 - 22.
7. Biagi E, Candela M, Turroni S, et al. Ageing and gut microbes: perspectives for health maintenance and longevity. Pharmacol Res. 2013; 69(1): 11- 20.
8. Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nat Med. 2016; 22(10): 1079 - 1089.
9. Guinane CM, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Therap Adv Gastroenterol. 2013; 6(4): 295-308.
10. Kelly JR, Kennedy PJ, Cryan JF, et al. Breakingdown the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front Cell Neurosci. 2015; 9: 392.
11. Kishikawa H, Nishida J, Nakano M, et al. Ulcerative colitis associated with aplastic anemia. Dig Dis Sci. 2003; 48(7): 1376-9.
12. Sharma BC, Yachha SK, Mishra RN, et al. Hypoplastic anemia associated with ulcerative colitis in a child. J Pediatr Gastroenterol Nutr. 1996; 23(3): 326-8.
13. Allegra A, Innao V, Allegra AG, et al. Role of the microbiota in hematologic malignancies. Neth J Med. 2019; 77(2): 67-80.
14. D'Angelo G. Role of hepcidin in the pathophysiology and diagnosis of anemia. Blood Res. 2013; 48(1): 10–5.
15. Peyssonnaux C, Zinkernagel AS, Datta V, et al. TLR4-dependent hepcidin expression by myeloid cells in response to bacterial pathogens. Blood. 2006; 107(9): 3727-32.
16. Khan FA, Fisher MA, Khakoo RA. Association of hemochromatosis with infectious diseases: expanding spectrum. Int J Infect Dis. 2007; 11(6): 482-7.
17. Orf K, Cunnington AJ. Infection-related hemolysis and susceptibility to Gram-negative bacterial co-infection. Front Microbiol 2015; 6: 666.
18. Ohkawara Y, Bamba M, Nakai I, et al. The absorption of iron from the human large intestine. Gastroenterology. 1963; 44: 611-4.
19. Johnston KL, Johnson DM, Marks J, et al. Non-haem iron transport in the rat proximal colon. Eur J Clin Invest. 2006; 36(1): 35-40.
20. Yilmaz B, Li H. Gut microbiota and iron: the crucial actors in health and disease. Pharmaceuticals (Basel). 2018; 11(4):98.
21. Kaur N, Chen CC, Luther J, et al. Intestinal dysbiosis in inflammatory bowel disease. Gut Microbes. 2011; 2(4): 211-6.
22. Jaeggi T, Kortman GA, Moretti D, et al. Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants. Gut. 2015; 64(5):731-42.
23. Swinkels DW, Tjalsma H, et al. Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants. Gut. 2015; 64(5): 731-42.
24. Frawley ER, Fang FC. The ins and outs of bacterial iron metabolism. Mol Microbiol. 2014; 93(4): 609-16.
25. Cremonesi P, Acebron A, Raja KB, et al. Iron absorption: Biochemical and molecular insights into the importance of iron species for intestinal uptake. Pharmacol Toxicol. 2002; 91(3): 97-102.
26. Cines DB, Liebman H, Stasi R. Pathobiology of secondary immune thrombocytopenia. Semin Hematol. 2009; 46 (1 Suppl 2): S2-14.
27. Assinger A. Platelets and infections - An emerging role of platelets in viral infection. Front Immunol. 2014; 5: 649.
28. Pockros PJ, Duchini A, McMillan R, et al. Immune thrombocytopenic purpura in patients with chronic hepatitis C virus infection. Am J Gastroenterol. 2002; 97(8): 2040-5.
29. Kaser A, Brandacher G, Steurer W, et al. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. Blood. 2001; 98(9):2720-5.
30. D'Angelo G. Inflammation and coagulation: a "continuum" between coagulation activation and prothrombotic state. J Blood Disord. 2015; 2: 1023 - 1027.
31. Hasan RA, Koh AY, Zia A. The Gut Microbiome and Thromboembolism. Thromb Res. 2020; 189: 77-87.
32. Vinchi F. Thrombosis Prevention: Let's drug the microbiome! HemaSphere, 2019; 3(1): e165.

33. Lou KJ. B cell lymphoma and the microbiome. SciBX. 2013; 31(6); 812.
34. O'Rourke JL. Gene expression profiling in Helicobacter-induced MALT lymphoma with reference to antigen drive and protective immunization. J Gastroenterol Hepatol. 2008; 23 Suppl 2: S151–6.
35. Banks PM. Gastrointestinal lymphoproliferative disorders. Histopathology. 2007; 50(1): 42-54.
36. Isaacson PG, Du MQ. MALT lymphoma: from morphology to molecules. Nat Rev Cancer. 2004; 4(8): 644-53.
37. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, et al. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. Lancet. 1991; 338(8776): 1175-6.
38. Bayerdorffer E, Neubauer A, Rudolph B, et al. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of Helicobacter pylori infection. MALT Lymphoma Study Group. Lancet. 1995; 345(8965): 1591- 4.
39. O'Rourke JL, Dixon MF, Jack A, et al. Gastric B-cell mucosa-associated lymphoid tissue (MALT) lymphoma in an animal model of 'Helicobacter heilmannii' infection. J Pathol. 2004; 203(4): 896- 903.
40. Schöllkopf C, Melbye M, Munksgaard L, et al. Borrelia infection and risk of non-Hodgkin lymphoma. Blood. 2008; 111(12): 5524-9.
41. Chang CM, Landgren O, Koshiol J, et al. Borrelia and subsequent risk of solid tumors and hematologic malignancies in Sweden. Int J Cancer. 2012; 131(9): 2208-9.
42. Marcotte EL, Ritz B, Cockburn M, et al. Exposure to infections and risk of leukemia in young children. Cancer Epidemiol Biomarkers Prev. 2014; 23(7): 1195-203.
43. Olszak T, An D, Zeissig S, et al. Microbial exposure during early life has persistent effects on natural killer T cell function. Science. 2012; 336(6080): 489- 93.
44. Lim ES, Zhou Y, Zhao G, et al. Early life dynamics of the human gut virome and bacterial microbiome in infants. Nat Med. 2015; 21(10): 1228-34.
45. Laforest-Lapointe I, Arrieta MC. Patterns of early-life gut microbial colonization during human immune development: an ecological perspective. Front Immunol. 2017; 8: 788.
46. Torow N, Hornef MW. The neonatal window of opportunity: setting the stage for life-long host–microbial interaction and immune homeostasis. J Immunol. 2017; 198(2): 557-563.
47. Haas, OA. Primary immunodeficiency and cancer predisposition revisited: embedding two closely related concepts into an integrative conceptual framework. Front Immunol. 2019; 9: 3136.
48. Ajrouche R, Rudant J, Orsi L, et al. Childhood acute lymphoblastic leukaemia and indicators of early immune stimulation: the Estelle study (SFCE). Br J Cancer. 2015; 112(6):1017-26.
49. Chang, JS, Tsai CR, Tsai YW, et al. Medically diagnosed infections and risk of childhood leukaemia: a population-based case-control study. Int J Epidemiol. 2012; 41(4): 1050- 9.
50. Rudant J, Lightfoot T, Urayama KY, et al. Childhood acute lymphoblastic leukemia and indicators of early immune stimulation: a Childhood Leukemia International Consortium study. Am J Epidemiol. 2015; 181(8): 549-62.
51. Blaser MJ. Antibiotic use and its consequences for the normal microbiome. Science. 2016; 352(6285): 544-5.
52. Wen Y, Runming J, Hongbo C. Interaction between gut microbiota and acute childhood leukemia. Front Microbiol. 2019;10:1300.
53. Tylavsky FA, Smith K, Surprise H, et al. Nutritional intake of long-term survivors of childhood acute lymphoblastic leukemia: evidence for bone health interventional opportunities. Pediatr Blood Cancer. 2010; 55(7): 1362-9.
54. Badr H, Paxton RJ, Ater JL, et al. Health behaviors and weight status of childhood cancer survivors and their parents: similarities and opportunities for joint interventions. J Am Diet Assoc. 2011; 111(12): 1917- 23.
55. Fuemmeler BF, Pendzich MK, Clark K, et al. Diet, physical activity, and body composition changes during the first year of treatment for childhood acute leukemia and lymphoma. J Pediatr Hematol Oncol. 2013; 35(6): 437-43.
56. Zhang FF, Saltzman E, Kelly MJ, et al. Comparison of childhood cancer survivors' nutritional intake with US dietary guidelines. Pediatr Blood Cancer. 2015; 62(8): 1461-7.
57. Duncan CN, Brazauskas R, Huang J, et al. Late cardiovascular morbidity and mortality following pediatric allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2018; 53(10): 1278-1287.
58. Chua LL, Rajasuriar R, Azanan MS, et al. Reduced microbial diversity in adult survivors of childhood acute lymphoblastic leukemia and microbial associations with increased immune activation. Microbiome. 2017; 5(1): 35.
59. Sung L, Lange B, Gerbing R, et al. Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia. Blood. 2007; 110(10): 3532-9.
60. Kachlany SC, Schwartz AB, Balashova NV, et al. Anti-leukemia activity of a bacterial toxin with natural specificity for LFA-1 on white blood cells. Leuk Res. 2010; 34(6): 777-85.

61. Shan W, Bu S, Zhang C, et al. LukS-PV, a component of Panton-valentine leukocidin, exerts potent activity against acute myeloid leukemia in vitro and in vivo. Int J Biochem Cell Biol. 2015; 61: 20 -8.
62. Dai C, Zhang C, Sun X, et al. LukS-PV induces differentiation by activating the ERK signaling pathway and c-JUN/c-FOS in human acute myeloid leukemia cells. Int J Biochem Cell Biol. 2016; 76: 107 -14.
63. Shan W, Ma X, Deng F. Is LukS-PV a novel experimental therapy for leukemia? Gene. 2017; 600: 44-47.
64. Pflug N, Kluth S, Vehreschild JJ, et al. Efficacy of antineoplastic treatment is associated with the use of antibiotics that modulate intestinal microbiota. Oncoimmunology. 2016; 5(6): e1150399.
65. Gold JS, Bayar S, Salem RR. Association of Streptococcus bovis bacteremia with colonic neoplasia and extracolonic malignancy. Arch Surg. 2004; 139(7): 760-5.
66. Pepeljugoski CA, Morgan G, Braunstein M. Analysis of intestinal microbiome in multiple myeloma reveals progressive dysbiosis compared to MGUS and healthy individuals. Blood. 2019; 134 (Supplement 1): 3076.
67. Calcinotto A, Brevi A, Chesi M, et al. Microbiota-driven interleukin-17-producing cells and eosinophils synergize to accelerate multiple myeloma progression. Nat Commun 2018; 9(1): 4832.
68. Fredricks DN. The gut microbiota and graft-versus-host disease. J Clin Invest. 2019; 129(5): 1808 -1817.
69. Farhadfar N, Gharaibeh RZ, Lyon D, et al. Microbiota phylogenic analysis revealed decreased abundance of Faecalibacterium prausnitzii, an anti-inflammatory commensal bacterium, in patients with chronic graft-versus-host disease. Hematol Oncol Stem Cell Ther 2021; 14(3):263-265.
70. Jenq R, Taur Y, Devlin SM, et al. Intestinal Blautia is associated with reduced death from Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2015; 21(8): 1373-83.
71. Gerbitz A, Schultz M, Wilke A, et al. Probiotic effects on experimental graft-versus-host disease: let them eat yogurt. Blood. 2004; 103(11):4365-7.
72. Ladas EJ, Bhatia M, Chen L, et al. The safety and feasibility of probiotics in children and adolescents undergoing hematopoietic cell transplantation. Bone Marrow Transplant. 2016; 51(2): 262-6.
73. DeFilipp Z, Peled JU, Li S, et al. Third-party fecal microbiota transplantation following allo-HCT reconstitutes microbiome diversity. Blood Adv. 2018; 2(7): 745-753.
74. Lehouritis P, Cummins J, Stanton M, et al. Local bacteria affect the efficacy of chemotherapeutic drugs. Sci Rep. 2015; 5: 14554.
75. Cheng WY, Wu CY, Yu J. The role of gut microbiota in cancer treatment: friend or foe?. Gut. 2020; 69(10): 1867-1876.
76. West NR, Powrie F. Immunotherapy not working? Check your microbiota. Cancer Cell. 2015; 28(6): 687 -689.
77. Shi Y, Zheng W, Yang K, et al. Intratumoral accumulation of gut microbiota facilitates CD47-based immunotherapy via STING signaling. J Exp Med. 2020; 217(5): e20192282.
78. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018; 359(6371):97-103.
79. Davar D, Dzutsev AK, McCulloch JA, et al. Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients. Science. 2021; 371(6529):595-602.