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CORRELATION BETWEEN HEMATOLOGY AND THE HUMAN MICROBIOME

M.E.B. Baladad[1,4], H.M. Basilio[2,4], J.B. Gomez-Pascual[3,4]

[1]College of Medical Laboratory Science, LORMA Colleges, Inc., City of San Fernando, La Union, Philippines
[2]Department of Health, Newborn Screening Center - Central Luzon, Angeles City, Pampanga, Philippines
[3]Laboratory Department, Immaculate Concepcion Polyclinic Hospital, Concepcion, Tarlac, Philippines
[4]Graduate School, Angeles University Foundation, Angeles City, Pampanga, Philippines

Corresponding Author: Mark Ericson Balagot Baladad, MMPHA, RMT; email: markericson.baladad@lorma.edu

Abstract – The crosslinked relationship between the human microbiome and the body's hematopoiesis has been observed in murine studies. This short review explores the emerging correlations between gut microbiome dynamics and hematological parameters, shedding light on the mechanisms that bridge these two complex systems and the potential implications for diagnosis, treatment, and prevention of blood-related diseases.

Keywords: Gut microbiota, Hematology, Hematopoiesis.

INTRODUCTION

The term "microbiome" refers to the wide array of microorganisms, including viruses, bacteria, fungal elements, archaea, and other single-celled organisms that inhabit the human body. Trillions of microbial cells with over a thousand species end in a symbiotic relationship with the human host, both beneficial to one another, given that the body is in a good health state[1]. Therefore, the gut microbiota can be considered a single functional organ that maintains proper bodily function.

In recent years, the human gut microbiome has emerged as a critical player in maintaining systemic health, extending its influence well beyond the gastrointestinal tract. Both systemic and localized processes and mechanisms include gut-to-brain communication, nutrient transformation, vitamin supply, maturation of mucosal immunity as well as tumor formation.

The bacterial composition of the gut microbiome is primarily dominated by the phyla *Firmicutes* and *Bacteroidetes*, with lesser proportions of *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*, among others, that live in a symbiotic relationship[2,3]. However, this varies greatly by individual and is influenced by diet, age, and health status[4]. Dysbiosis, or the alteration of the gut microbiome, has been shown to disrupt immune regulation, impair nutrient absorption, and contribute to various conditions, including inflammation, metabolic disorders, and hematological abnormalities.

In the context of hematology, hematopoiesis is defined as the body's systemic process of producing blood cellular components that occurs throughout embryonic growth, throughout adulthood, to replenish the entire body with blood. By understanding the entire process, hematopoiesis aids clinicians and researchers to fully comprehend the processes behind blood disorders and blood's function and response to any phenomenon.

SEARCH STRATEGY

The articles included in this review have been selected by following the inclusion and exclusion search criteria. Inclusion criteria: 1) articles concluded within the past decade, 2) published in a peer-reviewed, reputable, research journal, 3) have the full-text available and in open-access, and 4) are relevant to the topic at hand. Failure to meet this criterion has been resulted in the articles being deferred.

PATHOPHYSIOLOGIC MECHANISM

The gut microbiome plays a crucial role in hematological health by influencing the absorption of nutrients, particularly vitamins and minerals essential for blood formation and function. Key microbial populations assist in the synthesis and uptake of hematopoietic nutrients, such as vitamin B12, folate, and vitamin K, which are vital for erythropoiesis and coagulation[5]. Additionally, certain gut bacteria regulate iron homeostasis by modulating iron absorption and storage, thereby impacting the availability of iron for hemoglobin synthesis[6]. Alterations in microbial composition have been linked to a range of hematological disorders, including anemia, leukemia, thrombocytopenia, and even coagulopathies[7].

Another significant role is that they establish a variety of immune cell repertoires within the human body. This is crucial for our immune system to distinguish between pathogenic and non-pathogenic microorganisms. One of the investigated associations in recent years is the crucial role of the gut microbiota in normal hematopoiesis[8,9].

Lastly, the gut microbiome influences the immune landscape of the bone marrow, where blood cells are formed. Through the production of microbial metabolites such as short-chain fatty acids (SCFAs)—particularly butyrate—gut bacteria help maintain the integrity of the intestinal barrier and regulate systemic inflammation[10]. These metabolites interact with hematopoietic stem cells and immune cells, modulating their development and function.

Dysbiosis can lead to chronic inflammation, increased gut permeability (also known as “leaky gut”), and microbial translocation, all of which can trigger or exacerbate immune-mediated hematological disorders[11]. Thus, maintaining a balanced gut microbiome is critical for sustaining normal hematologic physiology[12].

DYSBIOSIS AND HEMATOPOIESIS

In dysbiosis, reduced levels of Short-Chain Fatty Acids (SCFAs) and increased gut permeability can lead to systemic inflammation and the translocation of microbial products, such as lipopolysaccharides (LPS), into the circulation, triggering immune responses that negatively affect hematopoietic stem cell (HSC) proliferation and skew hematopoiesis toward myeloid lineages, potentially contributing to conditions like anemia or leukocytosis[10].

Studies using germ-free (GF) mice have consistently shown that the absence of a gut microbiota leads to a significant reduction in both the number and size of hematopoietic progenitor cells (HPCs), suggesting a key role for microbial signals in sustaining hematopoiesis[13]. For instance, the results of a 2017 study demonstrated that colonization of GF mice with conventional microbiota restored HPC populations and immune cell counts, highlighting that microbial-derived factors such as short-chain fatty acids (SCFAs) and pattern recognition receptor (PRR) ligands are essential for proper hematopoietic development and immune system maturation[13].

Moreover, their T-cell function was also impaired alongside abnormal myeloid cells. One suggested mechanism is that dysbiosis promotes increased immunological activity in a specific area, causing inflammation. This will exert significant stress on the HPC levels that will result in their suppression[10].

Therefore, gut dysbiosis is associated with several diseases such as inflammatory bowel syndrome (ulcerative colitis and Crohn’s disease), necrotizing enterocolitis, in some cases of colorectal cancer, and several bacterial-associated diarrhea. Factors contributing to the imbalances in the gut microbiota diverge in the influence of nutrients, drugs, intestinal mucosa, immunity, as well as other stress aspects such as oxidative stress, bacteriophages, and bacteriocins[4].

As mentioned earlier, iron, vitamin B12, and folate are critical for the production of red blood cells (RBCs). The disruption of absorption caused by gut dysbiosis can result in anemia due to insufficient RBCs[6,14]. Additionally, dysbiosis can trigger chronic inflammation by increasing the levels of pro-inflammatory cytokines, which can impair both iron metabolism and immune function, potentially leading to a decrease in white blood cell (WBC) count. The altered gut microbiome may also contribute to the suppression of bone marrow activity, thereby further exacerbating the reduction in both red blood cell (RBC) and white blood cell (WBC) production. Additionally, dysbiosis often leads to increased intestinal permeability, allowing microbial products, such as lipopolysaccharides (LPS) to enter systemic circulation. These endotoxins can trigger chronic inflammation and immune activation, sometimes resulting in autoimmune-mediated platelet destruction, as observed in conditions such as immune thrombocytopenic purpura (ITP)[15,16].

SPECIFIC MICROORGANISMS AND HEMATOPOIESIS

Certain gut microorganisms play crucial roles in regulating hematopoiesis by producing bioactive metabolites and modulating immune signaling. Some murine studies were focused on recolonizing the microbiota in GF mice. One gut microbiota of interest is *Escherichia coli*[2]. The nucleotide-binding oligomerization domain-containing protein 1 ligand (NOD1L), which is a heat-resistant component of *E. coli*, was reported to restore the myeloid cell counts in the bone marrow of GF mice. The protein also has systemically increased the levels of stem cell factors and thrombopoietin, which are known HPC-proliferating cytokines. All of these factors promote normal hematopoiesis and can support the association of the gut microbiome and normal hematopoiesis[17].

Species within the *Firmicutes* phylum, such as *Clostridium butyricum* and *Faecalibacterium prausnitzii*, are well-known producers of butyrate, a short-chain fatty acid (SCFA) that supports hematopoietic stem cell (HSC) maintenance and promotes the anti-inflammatory environment necessary for balanced hematopoiesis. Butyrate enhances bone marrow niche health by influencing the expression of cytokines and adhesion molecules, thereby supporting stem cell renewal and lineage commitment. A reduction in these beneficial microbes during dysbiosis can compromise SCFA production, leading to hematopoietic dysregulation.

Additionally, *Bacteroides fragilis*, a member of the *Bacteroidetes* phylum, has been shown to exert immunomodulatory effects by producing polysaccharide A (PSA), which promotes the differentiation of regulatory T cells (Tregs) and suppresses excessive inflammation[18]. Through this mechanism, *B. fragilis* helps create a systemic immune environment that is conducive to normal HSC differentiation and function. In experimental models, colonization with *B. fragilis* restored bone marrow cell populations and corrected imbalances in myeloid *vs.* lymphoid lineages, which are often skewed under inflammatory conditions. This suggests that certain commensal bacteria have a direct influence on hematopoietic lineage outcomes by affecting systemic immune tone.

Moreover, *Lactobacillus* species, commonly found in the small intestine, have been shown to have positive effects on erythropoiesis and myelopoiesis. For example, supplementation with *Lactobacillus plantarum* has been associated with improved iron absorption and increased hemoglobin levels in anemic models, highlighting its potential therapeutic role in microcytic anemia. These bacteria enhance iron bioavailability by producing lactic acid, which lowers gut pH and improves iron solubility, thus supporting iron-dependent red blood cell production. Together, these studies underscore that hematopoiesis is not merely a bone marrow-contained process but is dynamically influenced by specific gut microbes and their metabolic and immunological interactions with the host[19].

MICROBIAL SIGNALING AND HEMATOPOIESIS

One suggested mechanism by which microorganisms affect hematology is through the release of signaling molecules. The signals are released by microbiota and are suggested to activate normal hematopoiesis. MyD88$^{-/-}$ and TICAM1$^{-/-}$ are signaling molecules, and a study

has heat-inactivated them, resulting in the non-expansion of the myeloid compartment in the bone marrow[20]. This data suggests their role in the appropriate signaling of the gut microbiome and bone marrow signaling. Another signaling molecule is Stat1-/- which prevented the further decrease of the granulocyte and HPC counts in antibiotic-treated mice suggesting its role in maintaining normal hematopoiesis. All of these signaling molecules are likely to be in the same biological pathway that regulates normal hematopoiesis[13,20].

ANTIBIOTIC USE AND HEMATOPOIESIS

Another aspect that researchers have explored is the effect of antibiotics on normal hematopoiesis. The problem arises when these medicines deplete not only the pathogenic microorganisms but also the microbiota. Thus, the use of antibiotics can profoundly disrupt the gut microbiome by reducing microbial diversity and depleting beneficial bacterial populations, which in turn can impair hematopoiesis.

Studies on mouse models have reported that antibiotic-treated or germ-free animals exhibit reduced numbers of hematopoietic stem and progenitor cells (HSPCs), altered immune cell development, and diminished bone marrow cellularity[13]. This is supported by another study wherein they performed *in vitro* culture of HPC and antibiotics. The result indicates that the antibiotics are not toxic to the HPC, thus providing evidence that the microbiota depletion affects the hematopoiesis and not the antibiotics themselves. Another study[21] reported patients developing neutropenia after using broad-spectrum antibiotics, and the majority of them have improved neutrophil counts after stopping antibiotic treatment.

This is largely due to the loss of microbial-derived signals, such as short-chain fatty acids (SCFAs) and pattern recognition receptor (PRR) ligands, that normally support the proliferation and differentiation of HSPCs. Furthermore, prolonged antibiotic use can lead to systemic inflammation due to gut barrier dysfunction, further disturbing the hematopoietic environment and potentially contributing to hematological imbalances, such as anemia, leukopenia, or skewed myelopoiesis.

CONCLUSIONS

Treating hematologic abnormalities by correcting gut dysbiosis involves restoring a healthy balance of gut microbiota through targeted interventions such as probiotics, prebiotics, dietary modifications, and, in some cases, fecal microbiota transplantation (FMT). Probiotics like *Lactobacillus plantarum* and *Bifidobacteria* can enhance iron absorption, reduce inflammation, and support red and white blood cell production by promoting the growth of beneficial microbes. Prebiotics, fibers that feed good bacteria, further encourage a favorable microbial environment. A diet rich in plant-based fibers, fermented foods, and low in processed sugars can help maintain this balance. In more severe or refractory cases, FMT may be considered to reintroduce a diverse and functional microbiota. Collectively, these approaches help restore microbial-derived signals critical for hematopoiesis, reduce systemic inflammation, and improve nutrient bioavailability, thereby supporting recovery from anemia, leukopenia, and related hematological conditions.

Conflict of Interests

All authors declare no conflict of interest.

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Authors' Contributions

All authors contributed to the conception and design of the scoping review. They collaboratively performed the literature search, screening, data extraction, and synthesis of findings. All authors reviewed and approved the final manuscript.

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ORCID

MEB Baladad: https://orcid.org/0009-0007-2112-3877
No ORCID is available for the other authors

Informed Consent

l participants provided their informed consent to take part in this study.

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