*hematology reports*

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*Review*

# Blood Microbiota and Its Products: Mechanisms of Interference with Host Cells and Clinical Outcomes

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**Abstract:** In healthy conditions, blood was considered a sterile environment until the development of new analytical approaches that allowed for the detection of circulating bacterial ribosomal DNA. Currently, debate exists on the origin of the blood microbiota. According to advanced research using dark field microscopy, fluorescent in situ hybridization, flow cytometry, and electron microscopy, so-called microbiota have been detected in the blood. Conversely, others have reported no evidence of a common blood microbiota. Then, it was hypothesized that blood microbiota may derive from distant sites, e.g., the gut or external contamination of blood samples. Alteration of the blood microbiota's equilibrium may lead to dysbiosis and, in certain cases, disease. Cardiovascular, respiratory, hepatic, kidney, neoplastic, and immune diseases have been associated with the presence of Gram-positive and Gram-negative bacteria and/or their products in the blood. For instance, lipopolysaccharides (LPSs) and endotoxins may contribute to tissue damage, fueling chronic inflammation. Blood bacteria can interact with immune cells, especially with monocytes that engulf microorganisms and T lymphocytes via spontaneous binding to their membranes. Moreover, LPSs, extracellular vesicles, and outer membrane vesicles interact with red blood cells and immune cells, reaching distant organs. This review aims to describe the composition of blood microbiota in healthy individuals and those with disease conditions. Furthermore, special emphasis is placed on the interaction of blood microbiota with host cells to better understand disease mechanisms.

**Keywords:** bacteria; blood microbiota; dysbiosis: extracellular vesicles; immune cells; lipopolysaccharides; outer membrane vesicles



**Citation:** Santacroce, L.; Charitos, I.A.; Colella, M.; Palmirotta, R.; Jirillo, E. Blood Microbiota and Its Products: Mechanisms of Interference with Host Cells and Clinical Outcomes. *Hematol. Rep.* **2024**, *16*, 440–453. https://doi.org/10.3390/hematolrep16030043

Academic Editors: Leona A. Holmberg and Claudio Cerchione

Received: 11 April 2024
Revised: 1 June 2024
Accepted: 18 June 2024
Published: 6 July 2024



## 1. Introduction

For many years, in the absence of specific diseases, blood was considered a sterile environment. However, the development of new analytical approaches, i.e., real-time PCR, allowed the detection of bacterial ribosomal DNA in healthy individuals [1]. Moreover, using techniques such as dark field microscopy, fluorescent in situ hybridization, and flow cytometry, pleiomorphic bacteria have been identified in the blood, forming the so-called blood microbiota or microbiome [2]. The microbiota refers to bacteria, viruses, and fungi, while the microbiome is a collection of genomes or genomic fragments, such as the DNA and/or RNA of microorganisms. Moreover, light and electron microscopy have revealed that the blood microbiota undergoes a few transformations in the context of peripheral blood mononuclear cells (PBMCs), such as vesiculation, tubulation, budding, and the protrusion of progeny cells from large electron-dense bodies [3]. Current research on healthy blood microbiota has documented that the *Bacillota*, *Actinomycetota*, *Pseudomonadota*, and

*Bacteroidota* phyla are dominant [4–6]. Microbial DNA detected in the blood of healthy subjects coexists in harmony with the host and exhibits immunomodulatory phenotypes. Their absence or presence may determine health or disease (sepsis) conditions [7]. Conversely, recent research based on the characterization of DNA signatures in the blood of 9.770 healthy individuals indicated no evidence of a common blood microbiota [8]. These findings suggest a transient process of commensal microbes' translocation to the bloodstream from other sites. Others have suggested that blood microbiota may derive from microbial contamination in low-biomass samples and that the undetermined viability of blood microbiota depends on culture-independent procedures [9,10]. In this framework, there is a general debate on the source of blood microbiota. According to more recent views, it may directly derive from gut microbiota or the skin–oral–gut axis [11,12].

Maternal origin of the blood microbiota cannot be ruled out, since its presence has been found in certain prenatal tissues, such as umbilical cord blood, meconium, amnion, and the placenta [13]. In recent years, some research has suggested the hypothesis that a certain combination of bacteria in the placenta may have an important role in premature births. In addition, periodontal disease in pregnant women may be associated with an increased probability of premature births. This hypothesis, although intriguing in light of the well-known correlation between oral disease and preterm birth, also highlights the importance of oral hygiene during pregnancy as a preventative practice for pregnant women. According to more recent studies, the presence of a placental microbiota has been denied, whereas placental asepticity has been confirmed. These findings reinforce the idea that the fetus lives in a sterile environment that allows for metabolic exchanges with the maternal blood, recalling the hypothesis that first contact with bacteria occurs during childbirth through the birth canal.

Although this research requires more in-depth analysis and methodological refinement, the mechanisms behind the maternal transfer of blood microbiota are still unknown, despite proposals of oral and gut fetal compartment colonization or the fetal ingestion of amniotic fluid during gestation [14–16].

Interestingly, blood microbiota sequencing studies have demonstrated differences according to geographical areas. For instance, Germany and Poland are characterized by higher blood microbiota values, with intermediate levels seen in Italy and Finland, and lower levels in Belgium and Austria [17]. Differences in bacterial DNA distribution may rely on hosts' genetic and immune factors or diet, hygienic factors, and parasitic loads [18–20]. It appears that the environment may have a greater impact than age, even if an association between blood microbiota and senescence cannot be excluded [21].

The persistence of microbes in the blood can cause several diseases involving the cardiovascular system, liver, and kidneys [21,22]. Compared to the gut, the blood microbiota can interact with the host to different extents, especially with leukocytes whose responses may determine disease status. Moreover, in healthy humans, the blood microbiota interacts with host cells via an array of products, e.g., metabolites, lipoglycans, quorum-sensing peptides, proteins, and bacterial extracellular vesicles (EVs) [23]. Outer membrane vesicles (OMVs) produced by Gram-negative bacteria are enriched in lipopolysaccharides (LPSs) and membrane proteins [24]. It is well known that LPSs are key molecules that interact with Toll-like receptors (TLR)-4 on monocytes and endothelial cells, activating the NF-kB pathway with the subsequent release of proinflammatory cytokines [25,26]. On the other hand, LPS micelles can be tolerated by the immune system, thus becoming innocuous to the host [27].

The disturbance of a core healthy microbiota in the blood may contribute to disease outcomes. In patients with myocardial infarction (MI) and chronic coronary syndrome, microbial diversity was reported to be higher than healthy individuals [28,29]. Liver fibrosis and cirrhosis are characterized by diverse blood microbiota. Certain bacteria provoke the release of proinflammatory cytokines and nitric oxide [30,31]. In kidney disease, circulating bacteria are not typical commensals of the urinary tract, thus suggesting their derivation from other sources, e.g., the gut [32,33]. In cancer, the blood microbiota

profile helps distinguish different cancer types and predicts the response to advanced colon cancer [34,35]. In patients with autoimmune disease, immunosuppression, HIV, and inflammatory bowel disease (IBD), blood bacteria have also been detected. However, it is unclear whether bacteria are the causative agents of disease or are provoked by disease outcomes [36–39].

The objectives of the present review include describing the blood microbiota composition in either healthy individuals or sick subjects. Furthermore, illustrating blood microbiota/host cell interaction will help to better understand the pathogenic mechanisms elicited by blood microbiota.

## 2. Data Selection

A comprehensive analysis of the current literature, searching related biological and clinical data on Scopus, Clarivate Analytics/Web of Science, PubMed, and EMBASE, as well as using the 'cited by' and 'similar articles' options available in PubMed, was carried out to prepare this review. All relevant data, mainly from original articles and clinical trials, were extracted and reported after a critical appraisal process by two independent authors (I.A.C. and M.C.).

## 3. Healthy Blood Microbiota

The concept of blood microbiota has been accepted, though controversial. According to some researchers, the blood microbiota naturally exists from birth throughout life, consisting of unharmful organisms living in equilibrium with the host [40,41]. Others have identified circulating microbial cell-free DNA in the blood or microbial vesicles containing metabolites and fragmented DNA or RNA [42–44]. Conversely, other groups deny the existence of blood microbiota [45,46]. Researchers who support blood microbiota existence have no consensus on its composition. *Staphylococcus* spp. is a common genus detected in the blood, but information at the species level is very poor [47–49]. *Pseudomonadota* phylum and *Cutibacterium acnes* are also found in the blood [50,51]. Bacterial diversity varies between the buffy coat, red blood cells, and plasma with 117 blood microbial species, including 110 bacteria, 5 viruses, and 2 fungi. These data point to the absence of a core healthy blood microbiota, with transient and sporadic translocation of commensals into the circulation. These commensals are rapidly cleared out and do not colonize. Recently, electron microscopy has contributed to blood microbiota research. Circulating microbiota in PBMCs from healthy donors undergo complex life cycles, involving different morphological transformations [52]. Blood microbiota can reproduce by irregular binary fission, budding, protrusion–extrusion of progeny cells from large electron-dense bodies, vesiculation, tubulation, or a combination of all types. The morphology of blood microbiota supports the existence of microorganisms in the blood of healthy people.

Blood microbiota profiles are assessed in healthy individuals or in patients to identify genetic signatures for risk stratification, diagnosis, disease surveillance, as well as drug development. However, the existence of human blood microbiota is still debatable, considering two major issues: high-risk contamination in low-biomass samples and the undetermined viability of blood microbiota via culture-independent profiling methods [53].

## 4. Dysbiosis of Blood Microbiota and Disease Outcome

Many factors influence the composition of the blood microbiota, such as leaking epithelial junctions, mucosal disruption, periodontal disease, chewing, and tooth brushing [52,54,55]. Alteration of the blood microbiota equilibrium may result in dysbiosis, which, in turn, may cause several diseases and induce a state of low-grade inflammation. Chronic low-intensity inflammation is a condition defined in recent years as one that can develop pathophysiologically for a long period without symptoms and then trigger even serious diseases. Although there are no specific tests to allow diagnosis, suspicion is possible through careful collection of the patient's medical history. In the following sections, blood

bacteria in the pathogenesis of cardiovascular, respiratory, hepatic, and kidney diseases as well as cancers and immune diseases are discussed.

### *4.1. Cardiovascular Diseases*

Bacteria, fragments, and their DNA have been identified in cardiovascular disease patients [56–59]. Importantly, LPS from blood bacteria participates in the atherosclerotic process via the formation of macrophage-derived foam cells [60–62].

*Pseudomonadota*, *Actinomycetota*, *Cyanobacteria*, and *Verrucomicrobia* from the circulating microbiota play a role in cardiovascular disease outcomes, with the Proteobacteria phylum predominant in acute coronary patients [63–67]. In light of the above findings, dysbiosis of the human blood microbiota has been proposed as a marker for cardiovascular disease prediction.

Blood *Desulfobacterota* is increased in acute coronary syndrome but decreased in chronic coronary syndrome. *Desulfobacterota* can reduce sulfur compounds, thus contributing to butyrate breakdown via the butyrate beta-oxidation pathway, maintaining the catabolic reaction's equilibrium [68,69]. *Desulfobacterota* also releases LPS, promoting atherosclerotic progression.

Elevated amounts of both *Escherichia* and *Shigella*, associated with high levels of interleukin (IL)-8, have been detected in coronary artery disease patients [70]. LPS from these bacteria likely cause inflammation via TLR or the inflammasome pathway, contributing to the pathogenesis of chronic coronary syndrome [71].

A higher abundance of *Bifidobacterium* and reduced numbers of *Bacteroidota* were detected in MI patients' blood [72]. MI patients' diverse blood microbiota composition can be attributed to various factors, such as geographic region, type of diet, genetics, and environmental changes [73]. Of note, blood bacteria associated with cholesterol and lipid metabolism are reduced in MI patients, potentially favoring atherosclerosis [74]. Of note, among cholesterol-degrading bacteria belonging to the *Nocardiaceae* and *Aerocollaceae* families, *Gordonia*, *Propionibacterium*, *Chryseobacterium*, and *Rhodococcus* are the most common.

### *4.2. Respiratory Diseases*

Studies on blood microbiota in respiratory disease are scarce. *Bacteroides*, *Alistipes*, *Parabacteroides*, and *Prevotella* are predominant in the blood, with a decrease in *Actinobacter*, *Verrucomicrobia,* and *Cyanobacteria* [75]. When patients are subgrouped according to inflammatory subtypes, lung function, and corticosteroid therapy, differential blood bacteria profiles allow accurate asthma diagnosis with elevated sensitivity and specificity. Moreover, through RNA-sequencing of peripheral blood samples, the genera *Acinetobacter*, *Serratia*, *Streptococcus*, and *Bacillus* have been associated with severe dyspnea in former and current smokers [76–78]. Interestingly, certain genera, such as *Streptococcus*, *Cutibacterium*, *Corynebacterium*, *Lactobacillus*, *Staphylococcus*, and *Bacillus* activate oxidative phosphorylation, mTOR, and Wnt/Beta-catenin pathways in circulating cells [79]. Similarly, blood *Escherichia coli*, *Bacillus* spp., *Campylobacter hominis*, *Pseudomonas* spp., *Thermoanaerobacter pseudethanolicus*, *Thermoanaerobacterium thermosaccharolyticum*, and *Staphylococcus epidermis* detection is correlated with severe COVID-19 [80–82].

### *4.3. Liver Diseases*

Liver fibrosis and cirrhosis are responsible for the abundance of diverse gut-derived circulating bacteria [83,84]. In this respect, the genus *Bacteroides* and the family *Enterobateriaceae* are more elevated in the blood of cirrhotic patients than in healthy individuals [85,86].

From a pathogenic point of view, certain circulating bacteria, i.e., *Corynebacteriales*, are inversely associated with gamma-interferon, IL-17A, and tumor necrosis factor (TNF)-alpha and may predict the reversal of portal hypertension in hepatitis C virus (HCV)-induced cirrhosis upon termination of antiviral treatment [87]. The presence of circulating LPSs in HCV patients supports the above data, with resulting endotoxemia contributing to inflammatory damage via the release of proinflammatory cytokines [88–92].

### *4.4. Kidney Diseases*

Evidence suggests that blood microbiota dysbiosis plays a role in chronic kidney disease (CKD). An inverse correlation between glomerular filtration rate and an increase in circulating *Pseudomonadota* has also been documented [93]. The genus *Devosia* in the blood appears to predict increased mortality risk in CKD patients on peritoneal dialysis with or without vascular calcification [94]. Furthermore, blood *Legionella* was elevated in IgA nephropathy patients, with putative involvement in kidney impairment and mortality [95]. It is worth noting that blood bacteria implicated in kidney diseases are not of urinary origin, suggesting that urinary mucosa alterations may not participate in blood microbiota dysbiosis [96].

### *4.5. Neoplastic Diseases*

In a recent study, microbiome analysis of blood and tissue revealed sequence reads not mapped to the human genome; rather, they belong to microorganisms such as bacteria, archaea, and viruses [97]. In this context, the blood microbiota profile of cancer patients helped distinguish different cancer types at very early stages, e.g., hepatocellular carcinoma, myeloid cancer, and gastric cancer [98–100]. Furthermore, bacterial genetic material in the blood could predict the cancer therapy response. Among patients with advanced colorectal cancer being treated with oxaliplatin/capecitabine/adoptive T cell immunotherapy, responders exhibited lactobacilli and the genera *Bifidobacterium* and *Enterococcus* more abundantly than non-responders [101]. Similarly, the genera *Lewinella* and *Paludibaculum* predicted a better clinical response to nivolumab in a non-small cell lung carcinoma patient [102]. Specific beta-glucoronidase and/or beta-galactosidase microbes in the gut regulate estrogen metabolism and the so-called estrobolome. Their increase has been associated with a higher risk of estrogen receptor-positive breast cancer in post-menopausal women [103,104]. In the blood, beta-glucuronidase-producing bacteria were predominant in breast cancer patients, while beta-galactosidase bacteria were predominant in healthy subjects [105]. Importantly, treatment of estrogen-receptor positive breast tumor cells with tamoxifen, an anti-estrogen, and *Staphylococcus aureus* EVs suppressed the AKT and ERK oncogenic pathways, causing more cell death [106]. Evidence suggests that *Staphylococcus* is reduced in breast cancer patients. In summary, the reported data suggest that the blood microbiota may play a role in cancer diagnosis, prognosis, and therapy.

### *4.6. Immune and Inflammatory Diseases*

In autoimmune diseases, blood microbiota dysbiosis may play a pathogenic role. Elevated blood levels of the genera *Desulfoconvexum*, *Desulfofrigus*, *Desulfovibrio*, *Draconibacterium*, *Planococcus*, and *Psychrilyobacter* and the phylum *Gemmatimonadetes* have been identified in patients with systemic lupus erythematosus (SLE). They are also associated with plasma autoantibody levels [107]. In vitro experiments that exposed PBMCs from SLE patients to heat-inactivated *Planococcus* released IL-1 beta, IL-6, and TNF-alpha, suggesting that this bacterium maintains an inflammatory status in circulation [108]. Similarly, rheumatoid arthritis (RA) abundance in the blood of *Halomonas* and *Shewanella* may be implicated in joint inflammation [109]. Evidence suggests that RA is associated with increased gut permeability; therefore, microbial translocation to the blood may account for inflammation [110]. These data suggest that RA outcomes provoke blood microbiota dysbiosis; however, dysbiosis, once established, may fuel the inflammatory process and promote disease progression.

In immunosuppressed patients who received liver transplantation, the families *Microbacteriaceae*, *Nocardiaceae*, and *Anelloviridae* were increased with a decrease in *Enterobacteriaceae* [111,112]. Furthermore, an association between an increase in *Xanthomonadaceae* and *Enterobacteriaceae* growth and acute host-versus-graft rejection was reported [113]. Opportunistic bacteria growth may be a side effect of immunosuppressant therapy; therefore, research in this direction may contribute to organ transplantation success. In the blood of patients with HIV, an increase in many genera, such as *Veillonella*, *Massilia*, *Haemophilus*,

*Arthrobacter*, and *Fusobacterium*, was observed. Furthermore, in vitro coculture of HIV+ PBMcs with *Massilia* and *Haemophilus* led to a massive release of proinflammatory cytokines [114]. These data suggest that in HIV patients' blood, dysbiosis may exacerbate disease progression. In inflammatory bowel disease, plasma EVs aggravate the inflammatory status and increase *Escherichia/Shigella* numbers in the blood [115]. These data are supported by the notion that circulating LPSs have been detected in patients with IBD, aggravating pre-existing inflammatory conditions [116]. In a feces-induced peritonitis porcine model, the emergence of new circulating bacteria was revealed, including *Escherichia/Shigella*, *Staphylococcus*, *Cloacibacterium*, *Diaphorobacter*, *and Rhodanobacter* [117]. These bacteria are related to ABC transporters and oxidative phosphorylation, which may sustain the pathogenesis of peritonitis. Additionally, patients with acute pancreatitis have shown a severe depletion of the phylum *Actinobacteria* and an increase in *Bacteroidota* compared to healthy subjects [118]. In patients with large vessel vasculitis, changes in blood microbiota composition have been detected in terms of elevation of the classes *Cytophagia* and *Clostridia* compared to healthy subjects [119]. These data indicate the pathogenic role of blood microbes in host inflammatory conditions.

In Table 1, the predominant blood microbiota in various diseases is illustrated.

**Table 1.** The components of blood microbiota associated with various diseases in humans.

| Blood Microbiota and Pathologic Conditions | |
|---|---|
| **DISEASES** | **Associate Bacterial Species** |
| CARDIOVASCULAR | - *Pseudomonadota* and *Desulfobacteria* ----> coronary disease;<br>- *Escherichia-Shigella* ----> coronary disease ---> IL-8;<br>- Increase in *Bifidobacterium* and decrease in *Bacteroidota* and bacteria associated with cholesterol and lipid excess in myocardial infarction; |
| RESPIRATORY | - Increase in *Bacteroides*, *Alistipes*, *Parabacteroides*, and *Prevotella*, and a decrease in *Actinobacter*, *Verrucomicrobia,* and *Cyanobacteria;* |
| LIVER | - Increase in *Bacteroides* and *Enterobacteriaceae* in cirrhotic patients;<br>- Increase in *Corynebacteriales* ----> reversal of portal hypertension in HCV patients; |
| KIDNEY | - *Devosia* products ----> increase in mortality risk in CKD patients;<br>- Increase in *Legionella* spp. in IgA nephropathy patients; |
| NEOPLASTIC | - Increase in *Bifidobacterium* and *Enterococcus* ----> distinction of different cancer types and prediction of response to therapy;<br>- Increase of beta-glucuronidase-producing bacteria in breast cancer patients; |
| IMMUNE | - Increase in *Desulfoconvexum*, *Desulfofrigus*, *Draconibacterium*, *Planococcus,* and *Psychrilyobacter* in SLE patients;<br>- Increase in *Halomonas* and *Shewanella* in RA patients;<br>- Increase in *Anelloviridae*, *Nocardiaceae*, and *Microbacteriaceae* and decrease in *Enterobacteriaceae* in liver transplanted patients;<br>- Increase in *Veillonella*, *Massilia*, *Haemophilus*, *Arthrobacter,* and *Fusobacterium* ----> proinflammatory cytokine release in HIV patients;<br>- Increase in *Escherichia/Shigella* in IBD. |

Abbreviations: HCV: Hepatitis C Virus; CKD: Chronic Kidney Disease; SLE Systemic Lupus Erythematosus; RA: Rheumatoid Arthritis; HIV: Human Immunodeficiency Virus; IBD: Inflammatory Bowel Disease.

## 5. Mechanisms of Interaction in Blood Microbiota with Host Cells

The microbiota belonging to mucosal sites, e.g., the respiratory system, gut, and urogenital tract, interacts with several epithelial cell types, including immune cells. Conversely, blood microbes make contact with red blood cells and leukocytes only. Bacteria are engulfed by macrophages and polymorphonuclear cells before their destruction by lytic enzymes. On the other hand, spontaneous binding of Gram-negative and Gram-positive bacteria to T lymphocytes has been demonstrated in vitro and in vivo in patients with typhoid fever [117–119]. According to the intensity of the stimulus, both phagocytes and

lymphocytes secrete various mediators that protect or damage the host. A weak stimulus cannot trigger immune reactions, so bacteria survive in full harmony with bacteria. Besides direct contact, bacteria mostly interact with PBMCs via their products. Once released into the bloodstream, LPS from the outer membrane of Gram-negative bacteria, lipoteichoic acid, peptidoglycans, and mycolic acids from Gram-positive bacteria activate immune cells via the production of proinflammatory cytokines and free radicals [120]. This process is upregulated in septicemia and endotoxemia characterized by elevated blood bacteria, as previously mentioned [121]. In this framework, microbiota-derived EVs have been detected in human blood from healthy volunteers [122]. They promote intercellular communication by carrying proteins, lipids, sugars, nucleic acids, and metabolites [123,124]. OMVs are an EV subtype produced by Gram-negative bacteria. They are natural proteo-liposomes with a double leaflet membrane containing bacterial metabolites, cytosolic proteins, and nucleic acids [125]. OMVs from *Pseudomonas aeruginosa* induce a potent innate immune response via LPS and protein components [126]. In healthy individuals, it has been hypothesized that OMVs derive from the gut following the disruption of epithelial cell tight junctions and then diffuse into the bloodstream, ultimately reaching distant organs [127]. LPS-bearing EVs have been detected via electron microscopy in leaky gut, and OMVs from *Bacteroides thetaiotamicron* can translocate from the intestinal epithelium to distant organs [128,129]. A recent study found that OMVs isolated from the red blood cells of healthy donors contained bacterial proteins and lipids [130]. The same study tracked the fusion of fluorescent *E. coli* EVs with PBMCs and discovered that EVs interacted with monocytes only. Furthermore, there is evidence that LPSs from *E. coli* OMVs can interact with TLR4 in monocytes but not with T cells, B cells, or γδ-2 unconventional T cells. These data suggest that bacterial EVs participate in the interaction between the blood microbiota and host cells, leading to the activation of the NF-kB pathway and the subsequent release of proinflammatory cytokines and free radicals.

The main mechanisms of the interaction between the blood microbiota and host cells are depicted in Figure 1.

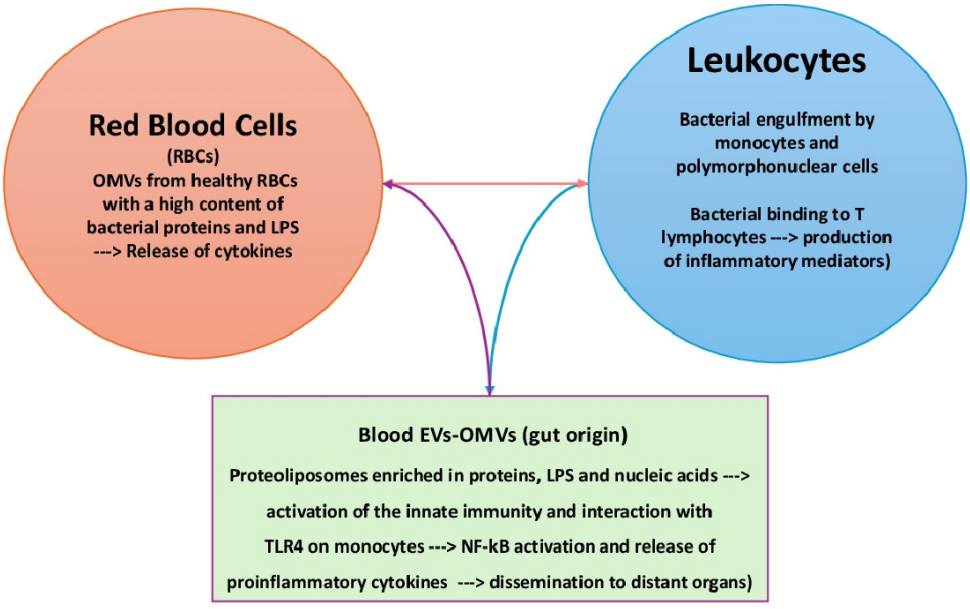


**Figure 1.** Interaction of the blood microbiota with host cells. Blood bacteria can directly interact with monocytes (engulfment) or T lymphocytes (binding). Bacterial products, e.g., EVs and OMVs, contain toxic products, such as LPSs, which can stimulate innate immunity and interact with TLR4 on monocytes. EVs: extracellular vesicles; OMVs: outer membrane vesicles.

Based on the data reported above, we can clearly affirm that systemic dysbiosis accounts for many pathologic conditions mediated by blood microbes. Conversely, commensal microbiota and restored eubiosis play an important role in host recovery.

## 6. Conclusions

Research on the blood microbiota requires further investigation since data are scarce and, sometimes, controversial. For instance, studies based on the bacteriome do not consider the viriome, archaeome, or mycobiome. Research on the blood microbiota is limited by these examples. To better understand the pathogenesis of various human diseases, the relationship between microorganisms from different kingdoms must be investigated. Current investigations into blood core bacteria are based on observational studies only, which indicate correlations but not causal relationships. Consequently, additional exploration should be carried out to decipher the disease mechanisms elicited by these core bacteria. Moreover, they originate from the host commensals, and diverse core bacteria have been observed in the same disease. In this regard, contrasting results about the existence and origin of fetal/placental microbiota, as determined by different sampling techniques and study methods, offer interesting definitions for the unborn child's microbiota acquisition mechanisms, the infection mechanisms in utero, and their consequences.

These findings suggest that diverse core microbiota may contribute to the pathogenesis of common diseases, indicating a redundancy of microbes in different communities, with a convergent evolution when exposed to similar environments. Therefore, pooling and meta-analyzing data from independent studies with appropriate adjustments to confounding variables is needed. In conclusion, evidence supporting a core healthy blood microbiota is still limited. However, microbial gene signatures may be of diagnostic, prognostic, and therapeutic value, prompting further studies and better validation of current data.

**Author Contributions:** Conceptualization: E.J. and L.S.; investigation: M.C. and I.A.C.; validation: R.P.; writing—original: E.J. and I.A.C.; resources: R.P.; project administration: L.S. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** All available data have been reported in the manuscript.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## Abbreviations

| | |
|---|---|
| CKD | Chronic Kidney Disease |
| EVs | Extracellular Vesicles |
| HCV | Hepatitis C Virus |
| IL | Interleukin |
| LPS | Lipopolysaccharides |
| MI | Myocardial Infarction |
| NO | Nitric Oxide |
| OMVs | Outer Membrane Vesicles |
| PBMCs | Peripheral Blood Mononuclear Cells |
| RA | Rheumatoid Arthritis |
| SLE | Systemic Lupus Erythematosus |
| TLR | Toll-like receptor |
| TNF | Tumor Necrosis Factor |

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