Transfusion and Apheresis Science 56 (2017) 330–335

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

The microbiome and transfusion in cancer patients

Hadi Goubran[a,*], Jerard Seghatchian[b,*], Julia Radosevic[c], Gaafar Ragab[d], Thierry Burnouf[e,f,*]

[a] Saskatoon Cancer Centre and College of Medicine, University of Saskatchewan, Saskatchewan, Canada
[b] International Consultancy in Blood Components Quality/Safety Improvement, Audit/Inspection and DDR Strategies, London, UK
[c] Human Protein Process Sciences, Aubers, France
[d] Rheumatology and Immunology Unit, Internal Medicine Department, Cairo University, Egypt
[e] Graduate Institute of Biological Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan
[f] International PhD Program in Biomedical Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan

ARTICLE INFO

Keywords:
Microbiome
Transfusion
Cancer

ABSTRACT

Our microbiota is determined by many variables including ABO blood groups. The microbiota is not only confined to the gut and skin but is also recoverable from blood of healthy donors.

The microbiota shape our immune system through cross reactivity with antigens, the expression of direct molecular patterns, the release of cytokines, the effects on nutrients and micronutrients and even through an interplay with epigenetics. It is likely, therefore, that a donor's microbiota could alter the antigenicity of blood and its components and potentially contribute to transfusion-related immune modulation [TRIM]. It could also potentially transmit infections. The recipient's microbiome contributes, on the other hand, to the tolerance to transfused blood, or to the development of transfusion reactions. Cancer patients are a particularly vulnerable population, often immunosuppressed with a significantly altered microbiota. They are more at risk for transmission of "dormant" bacteria via blood transfusion. Furthermore, chemotherapy and radiation induce mucositis that likely results in significant translocation of gut microbiota and abnormal immune reactions to transfused blood. It is therefore relevant to revisit transfusion thresholds and consider transfusion-saving strategies in cancer patients.

Contents

1. Introduction

A whole ecological community of commensal, symbiotic and pathogenic microorganisms literally share our body space. This complex symbiosis shaped who we are as, through our evolution, we acquired prokaryotic organelles and retroviruses integrated into our genomic material [1,2]. Gut and skin microbiota are known to alter and shape our immune response, in a genetically determined, ABO group-related manner, determining the differences in the profile in microbiota composition [3]. The study of the

* Corresponding authors at: Saskatoon Cancer Centre, 20 Campus Drive, S7N 4H4 Saskatoon, Canada.
E-mail addresses: hadi.goubranmessiha@saskcancer.ca (H. Goubran), jseghatchian@btopenworld.com (J. Seghatchian), thburnouf@gmail.com, thierry@tmu.edu.tw (T. Burnouf).

http://dx.doi.org/10.1016/j.transci.2017.05.023
1473-0502/

blood microbiome with "dormant bacteria" likely resulting from translocation of gut microbiota [4], most of which cannot be cultivated, is, on the other hand, an evolving field that will likely expand our knowledge in transfusion medicine. The introduction of metabolomics and proteomics (omics) to transfusion medicine [5] will allow for a better understanding of the donor/host variability and the role played by the microbiome.

It is likely that our microbiota affect the immune system shaping the antigenicity and potentially contributing to transfusion-related immune modulation [TRIM] as well as potential transmission of infection by donors. Whereas, the recipient's microbiome contributes to a certain level of tolerance to the transfused blood, or, by contrast, to the development of transfusion reactions.

Cancer patients are a particularly vulnerable population, often immunosuppressed, with a significantly altered microbiota. They should therefore be at higher risk for transmission of "dormant" bacteria via blood transfusion. Furthermore, chemotherapy and radiation induce mucositis that likely results in significant translocation of gut microbiota and abnormal immune reactions to transfused blood.

2. The microbiota

As humans we co-evolved with a wide variety of microorganisms that led to blurs in the distinction between self and non-self [1,2]. The skin and different body cavities are colonized by a plethora of microbes that include commensals (symbionts) and potential pathogens (pathobionts) ranging from bacteria and protozoa to fungi and viruses and even archaea [1]. The gut microbiota formed of all gut flora is the largest reservoir of commensals and is profoundly affected by our diet. It lives in a symbiotic relationship with its host influencing a wide variety of physiologic processes including nutrient availability, metabolism, immune system response and development, as well as hemostasis. It even affects our behavioural and psychiatric state [6–8]. The microbes outnumber human cells by a ratio of 10:1, with thousands of species isolated from humans [9,10].

The human microbiome and virome refers to the genome of our ecological community. The micro-animals that live on the human body are usually excluded [2]. Host-gut microbiota interact with environmental factors and other organisms including exogenous viruses [1]. Furthermore, bacteriophages within commensal bacteria modify them affecting the host by multiple mechanisms [1].

Perhaps the most classic example on how gut microbes affect our hemostatic system is the production of micronutrients, like vitamin K, by our gut bacteria. It was discovered in the 1980s that a fraction of vitamin K in humans is derived from menaquinone biosynthesis by the intestinal flora [11,12]. Moreover, the use of oral antibiotics such as cephalosporins, for example, is known to be associated with the development of hypoprothrombinemia. However, it has not been fully established whether these changes are induced by an inhibition of vitamin K production by intestinal microorganisms alone, or by an inhibitory action of these antibiotics on endogenous vitamin K metabolism as well [13]. Any compositional or functional disturbance of the microbiota, defined as "dysbiosis" is associated with a wide variety of morbidities ranging from inflammation to obesity, and from cardiovascular disease to autoimmunity and cancer [6].

With improved bacterial culture methods as well as the use of next generation sequencing techniques, recent research demonstrated that bacteria, including many known pathogens, can remain dormant in blood and within blood cells [14,15]. A plethora of non-communicable diseases in all aspects of medicine have been shown to be associated with a non-negligible bacterial component, sometimes detectable in blood [16–18]. This new paradigm—that healthy individuals harbour a rich microbiota in their blood—raises the question of the role of this microbiota and its impact on the risk associated with blood transfusion [4]. In their elegant study conducted on 30 healthy blood donors, Païssé et al. [4] set up a 16S rDNA quantitative polymerase chain reaction assay as well as a 16S targeted metagenomics sequencing pipeline specifically designed to analyze the blood microbiome, which was used on whole blood as well as on different blood fractions (buffy coat [BC], red blood cells [RBCs], and plasma). The distribution of 16SDNA spreads over a broad range among donors and most of the blood bacterial DNA was located in the BC (93.74%), whereas RBCs contained more bacterial DNA (6.23%) than the plasma (0.03%). Blood fractions contain bacterial DNA mostly from the Proteobacteria phylum (more than 80%) but also from Actinobacteria, Firmicutes, and Bacteroidetes and among the taxa that are significantly more present in RBCs, at least seven are genera (*Acinetobacter*, *Escherichia*/*Shigella*, *Corynebacterium*, *Pseudomonas*, *Staphylococcus*, *Stenotrophomonas*, and *Shewanella*) containing species that are pathogens known to infect human blood [4]. The blood microbiome therefore, is derived at least partially if not mostly from the gut microbiome as a result of several mechanisms of bacterial translocation [4,19]. It should be kept in mind that bacteria identified as blood microbiome could however result from artefactual contamination from reagents [20,21] or the introduction of bacterial contaminants during phlebotomy and sample manipulation [22].

Interestingly, an association between the ABO blood group and the human intestinal microbiota composition was reported [3] where the microbiota from the individuals harbouring the B antigen (secretor B and AB) differed from the non-B antigen groups and also showed higher diversity of the Eubacterium rectale-Clostridium coccoides (EREC) and Clostridium leptum (CLEPT) groups in comparison to other blood groups.

The impact of the microbiome can possibly affect blood directly through our blood microbiota but also indirectly through the interplay of the gut and body microbiota and the immune system, resulting in enhanced immunogenicity of specific donor units or enhanced or suppressed reactivity in specific recipients.

3. Microbiota/microbiome and immunity

Dysbiosis can modulate the host's innate and adaptive immune system [23]. According to the hygiene hypothesis, gnotobiotics (the rearing of animals under germ-free conditions, with or without subsequent exposure at various stages of postnatal life or adulthood to a microbial species or species consortium) results in an increased incidence of autoimmune diseases. In western countries, the increased prevalence of autoimmunity may be explained by changes in early microbial exposure, leading to altered immune maturation. Even more, children with microbiota that produce poorly immunogenic lipopolysaccharides are more at risk for autoimmunity [24]. It is known from metagenomic studies of the human gut microbiota/microbiome that early postnatal environment exposures are crucial in determining the phylogenetic structures of adult microbiota that are fully assembled by three years and often shared by family members [25,26].

Microbiota can affect the immune system as a result of cross reactivity of its structure with self-antigens, by directly affecting the immune system as a result of some of their molecular patterns or through nutrients and micronutrient alterations or through the stimulation of cytokines and hormonal mediators [1,23].

3.1. Antigen cross-reactivity

In view of the huge diversity, persistent colonization and high load of our microbiota, it is logical to presume that sharing peptide