

# Screening out the Exposome to Improve Transfusion Quality

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**R**ed blood cells (RBCs) play an essential role in the transport and delivery of oxygen to tissues. To accomplish this goal, approximately 90% of the dry weight of RBCs is composed of hemoglobin. However, proteomics studies have revealed that the remaining 10% is composed of a repertoire of approximately 3000 gene products.<sup>1</sup> As a result of this repertoire, RBCs are able to respond to environmental stimuli such as hypoxia and oxidant stress via metabolic reprogramming and posttranslational modifications.<sup>2,3</sup> These responses are triggered by direct stimulation of receptors on the RBC surface or through hemoglobin-oxygen saturation. Because RBCs contain several different receptors, including dopaminergic, purinergic, muscarinic, and other neurotransmitter-stimulated receptors, RBCs may be sensitive to small molecules which can affect cell metabolism and thus its ability to load and off-load oxygen.<sup>4</sup> RBCs have also been recently shown to directly metabolize certain drugs (Figure 1).

RBC transfusion is one of the most common procedures in modern medicine with over 100 million transfusions occurring worldwide every year. To accommodate such a common procedure, refrigerated RBC unit storage in blood banks is necessary and RBC units can be stored for up to 42 days in the United States. However, refrigerated RBC unit storage leads to the progressive accumulation of storage lesions which may affect the efficacy of transfusion. Omics technologies have been applied recently in the field of transfusion medicine to better understand factors influencing the storage lesion, which in turn impact RBC unit quality and transfusion efficacy. Important broad categories have emerged, including RBC unit storage bags and solutions, processing techniques, and blood donor biology.<sup>5-7</sup> Interestingly, blood donor factors including age, sex, ethnicity, donation frequency, and genetic polymorphisms such as glucose 6-phosphate dehydrogenase deficiency, have been demonstrated to influence the storage lesion.

Recently, there has been an active interest in studying how blood donor environmental exposures, known collectively as the “exposome,” can impact the RBC storage lesion in their donated units. Such exposures include medications and donor behaviors like alcohol use and smoking, amongst others. As an example, blood donor smoking has been associated with markers of oxidant stress like carboxyhemoglobin altered glutathione homeostasis, and in pilot studies, RBC units from smokers have been associated with reduced hemoglobin increments following transfusion.<sup>8-10</sup>

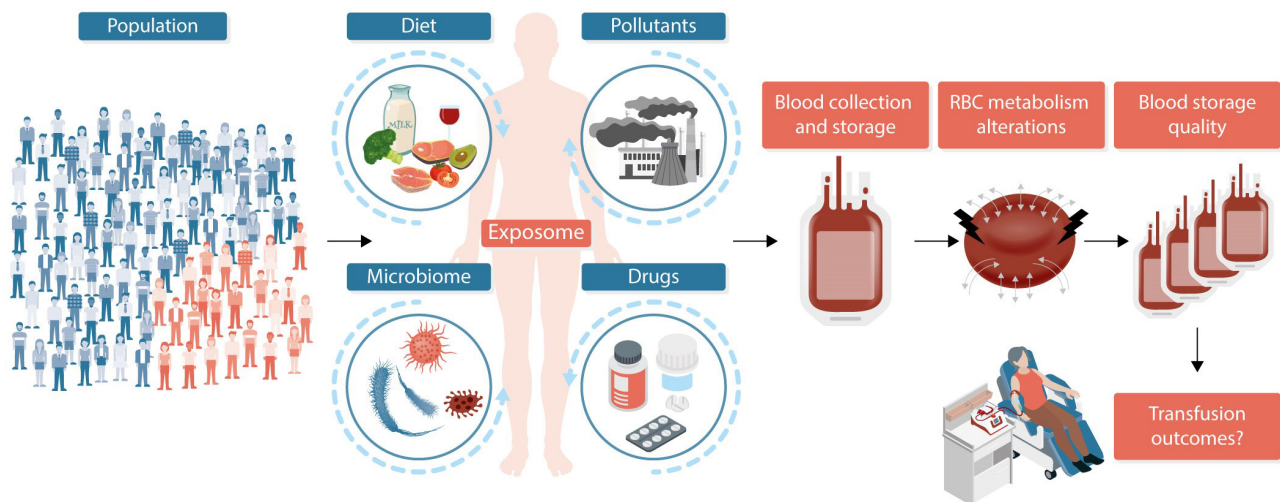
In a recent *JCI Insight* publication, Nemkov et al<sup>11</sup> conducted a series of preliminary experiments investigating the blood donor exposome, more specifically focusing on the impact of common medications on RBC metabolism. First, RBC units from 250 healthy blood donor volunteers were sampled at storage days 10, 23, and 42 for metabolomics analyses of the RBC exposome, a library of small molecule metabolites derived from the diet, microbiome, and xenometabolites such as pollutants or drugs. Examples of blood donor behaviors that emerged included alcohol use in 49.2%, smoking in 12.4%, and caffeine use in 39.6%. Looking at the most common prescription or over-the-counter medications in the United States, traces of almost every compound were detected in at least one donor included in the study. Examples of the most commonly detected classes of medications included Non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, progestins, statins, calcium channel and beta-blockers, type II diabetes medications, diuretics, and antacids. Blood donors on statins, angiotensin II receptor blockers, and antacids showed the greatest deviation in RBC energy and redox metabolic phenotypes from baseline.

High-throughput metabolomics analyses confirmed that U.S. Food & Drug Administration (FDA)-approved drugs directly impact RBC metabolism. Small molecule drugs were found to alter the levels of erythrocyte metabolites implicated in storage-related changes, including reduced glutathione, lactic acid, S-adenosyl-L-methionine, and hypoxanthine. To highlight one example of how medications can impact RBC metabolism, the authors focused on ranitidine, a histamine H<sub>2</sub> receptor antagonist. In RBCs, histamine positively regulates sphingosine kinase 1 (Sphk1), the rate-limiting enzyme of the synthesis of sphingosine 1-phosphate (S1P), a major regulator of RBC

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HemaSphere (2021) 5:7(e605).  
<http://dx.doi.org/10.1097/HS9.0000000000000605>.  
Received: 10 May 2021 / Accepted: 18 May 2021



**Figure 1. Impact of the exposome in transfusion medicine.** The exposure of the overall population, including blood donors, to a number of environmental stimuli such as pollutants and drugs, the choice of certain behaviors including food preferences, smoking and alcohol consumption, and the presence of a specific microbiome might impact red blood cell homeostasis by altering cell metabolism and oxidative status. These alterations can affect the quality of donated red blood cell units upon storage, with potentially suboptimal outcomes after transfusions. By identifying detrimental exposures and preventing or counteracting their effects we expect to enhance the safety and efficacy of transfusions.

glycolysis and function under physiological and pathological conditions. One blood donor in the study had ranitidine detected, and RBCs from this donor showed, as predicted, elevated S1P metabolism and S1P-regulated glycolysis with a decrease in several metabolic storage lesion markers, including markers of poor posttransfusion recovery such as hypoxanthine, arachidonic acid, and 12-hydroxyeicosatetraenoic acid. The authors further confirmed their findings by showing that ranitidine boosted S1P levels and glycolysis in a dose-dependent fashion in human and murine wild-type RBCs, but not in Sphk1-KO RBCs. Lastly, a proteome integral solubility alteration assay suggested a number of potential interactions of ranitidine with human RBCs, including hemoglobin subunits and several enzymes involved in redox homeostasis, glutathione synthetase, guanosine monophosphate metabolism, structural homeostasis, vesiculation, and protein degradation.

The authors' findings have several implications for the field of transfusion medicine. As the blood donor population ages in the United States, donors will progressively be exposed to more and more medications to maintain health. It is important to understand how drugs impact RBC physiology and metabolism as units from these donors are used routinely for transfusion. In their study, a striking 65.1% of FDA-approved medications showed a significant effect on RBC metabolism. Although the authors present an example of a medication that may enhance RBC storage, which can have implications for improving RBC storage and quality, it is also important to be mindful of medications with potential detrimental effects on RBC metabolism. Decreased transfusion efficacy has important implications for all patients, but especially for those receiving chronic transfusions throughout their lifespan such as in sickle cell disease or thalassemia. Every additional transfusion in these patients can be associated with alloantibody formation, which can make future blood more difficult to obtain, as well as transfusion reactions and increased iron overload. Although blood donor recruitment continues to be challenging, the age of personalized transfusion medicine is exhilarating, and these recent findings suggest that we will soon be able to provide units with enhanced efficacy and safety by screening out harmful donor exposures.

## Disclosures

The authors have no conflicts of interest to disclose.

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