Editorial

Benefits of hypoxic storage of red blood cells

Anastasios G. Kriebardis

Laboratory of Reliability and Quality Control in Laboratory Hematology (HemQcR), Department of Biomedical Sciences, School of Health & Welfare Sciences, University of West Attica Egaleo, Greece

Erythrocytes or red blood cells (RBCs) are unique cells that supply sufficient oxygen to tissues to fuel oxidative phosphorylation for efficient energy production. RBCs survive in the human circulation system for approximately 120 days. During this time, they accumulate oxidative damage and are promptly removed by the reticuloendothelial system.

Packed RBC storage in the blood bank is a logistic necessity, making approximately 100 million blood units available for transfusion every year worldwide. However, as RBCs are stored up to 42 days under refrigerated conditions (+4°C), whether after leukoreduction or not, they accumulate a series of biochemical and morphological changes, collectively referred to as the storage lesion[1]. The erythrocyte storage lesion is affected by biological (the genetic profile such as sex, G6PD, Hb traits) and environmental (donor age, diet, and smoking habits) factors. Such alterations are primarily driven by oxidant stress[2] and target redox sensitive metabolic enzymes[3] upstream to 2,3-diphosphoglycerate (DPG) and adenosine triphosphate (ATP) synthesis, thus resulting in the depletion of these metabolites. This phenomenon in turn alters RBC oxygen kinetics, due to the role of DPG and ATP in the modulation of hemoglobin allostery[4]. The RBC storage lesion results in decreased circulation and function of transfused erythrocytes.

Over the years, the Zimring lab has pioneered novel murine models of blood storage, the scope of which has been to show that genetic factors contribute to the heterogeneity of the onset and severity of the RBC storage lesion, ultimately reducing the capacity of the stored erythrocyte to circulate after transfusion as a function of redox system activity[5]. Murine models can check for genetic or environmental factors, and much interventional research can be carried out in mice that is neither technically feasible nor ethical in humans.

In parallel, studies in humans, which had received fresh impetus from the work of Bitensky and Yoshida[6], have posited that storage of RBC under oxygen-depleted conditions (hypoxia to anerobiosis) contributes to a Fenton and Haber-Weiss reaction, to the extent that these iron-dependent reactions fuel the generation of reactive oxygen species in the stored RBC[7]. Since these seminal observations, follow-up studies from the D'Alessandro lab have proved that hypoxic storage of RBCs reduces oxidation of glycolytic enzymes[8], hemoglobin at functional residues[9], decreases purine breakdown and deamination[10], preserves RBC morphology[11] and ultimately results in improved metabolic phenotypes and increased post-transfusion recovery[12]. Some of these benefits of hypoxic storage are not necessarily completely dependent on the prevention of oxygen radical formation. Indeed, they may, at least in part, be explained by the activating effect of alkalinization on rate-limiting

Correspondence: Anastasios G. Kriebardis
e-mail: akrieb@uniwa.gr

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enzymes of glycolysis and the Rapoport-Luebering shunt as a result of hypoxic and hypocapnic storage, i.e., upon concomitant removal of oxygen and carbon dioxide from the blood unit[13].

In this issue of *Blood Transfusion*, Hay and colleagues from the Zimring and D'Alessandro labs show for the first time that similar effects on oxygen-dependent metabolic reprogramming are observed in murine RBCs upon storage under hypoxic conditions[14]. They also show that, like in humans[12], a mitigated metabolic lesion also results in increased post-transfusion recoveries. The authors are to be commended for their clean experimental design. Here there is no speculation, but rather an appreciation of the caveats that are intrinsic to the extrapolation of results from any (animal) model to human biology/medicine.

Their study represents a breakthrough in that it paves the way for targeted investigations that could promote genetic or pharmacological manipulation in the context of normoxic or hypoxic storage and post-transfusion outcomes; such studies in humans are challenged by ethical and economical barriers. For example, this workflow that draws on both omics studies and murine models of post-transfusion recovery can be coupled to testing *in vivo* performance of RBCs upon storage in novel additive solutions. In parallel, while it is difficult to test the potential benefits of hypoxic storage in routine donors characterized by elevated susceptibility to oxidative hemolysis[15-17], such studies may be facilitated by a combination of the approaches described here by Hay and colleagues, along with the use of murine models of G6PD deficiency from the same groups[18].

This study contributes to our knowledge of the science of Transfusion Medicine and the erythrocyte storage lesion.

The Author declares no conflicts of interest.

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