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Research perspectives

Oxidative stress and antioxidant defenses during blood processing and storage of erythrocyte concentrates

Stress oxydatif et défenses antioxydantes durant le stockage des concentrés érythrocytaires

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Abstract

Oxidative lesions start accumulating in cells when the oxidant attacks overwhelm the antioxidant defenses. This review will briefly describe red blood cell storage lesions with emphasis on the consequences of oxidation and the cellular defense mechanisms, as well as the methods that can be used to monitor them. The sources of variability in red blood cell storage capacity depend on the donor characteristics, the product processing and the storage conditions. Suggestions to improve the product quality in order to ensure the best efficacy and safety for the transfused patient are also discussed.

Keywords: Red blood cells; Storage lesions; Oxidative stress; Antioxidants; Storage capacity

Résumé

Les lésions oxydatives commencent à s'accumuler dans les cellules lorsque les attaques des oxydants surpassent les défenses antioxydantes. Dans cette revue, les lésions de stockage des globules rouges seront brièvement décrites avec une emphase particulière sur les conséquences de l'oxydation et les moyens de défense cellulaires, ainsi que sur les méthodes pouvant être utilisées pour suivre leurs évolutions. Les sources de variabilité dans la capacité de stockage des globules rouges dépendent des caractéristiques du donneur, de la préparation du produit et des conditions de stockages. Quelques pistes permettant d'améliorer la qualité du produit, assurant ainsi la meilleure efficacité et sécurité pour le patient transfusé sont également discutées.

Mots clés : Globules rouges ; Lésions de stockage ; Stress oxydatif ; Antioxydants ; Capacité de stockage

1. Introduction

Stored red blood cells (RBCs) face conditions that diverge strongly from their natural environment. Indeed, after the donation, RBCs are separated from the other blood components by centrifugation and are suspended in an additive solution. They are then kept as an erythrocyte concentrate (EC) in a gas-permeable plastic bag, without agitation at 4 °C, until transfusion. These conditions are not physiological at all, and it is well known that RBCs accumulate various lesions (or behave differently than in vivo) during blood banking [1,2]. Important changes first appear at the level of the RBC metabolism [3], followed by the occurrence of oxidative stress (imbalance in the redox homeostasis) [4–8], which ultimately result in the alteration of the cell rheological properties [9] (Fig. 1). Some of these modifications may be reversible whereas others are irreversible. They can lead to the rapid clearance of the RBCs from the patient's bloodstream, thus decreasing the beneficial impact of

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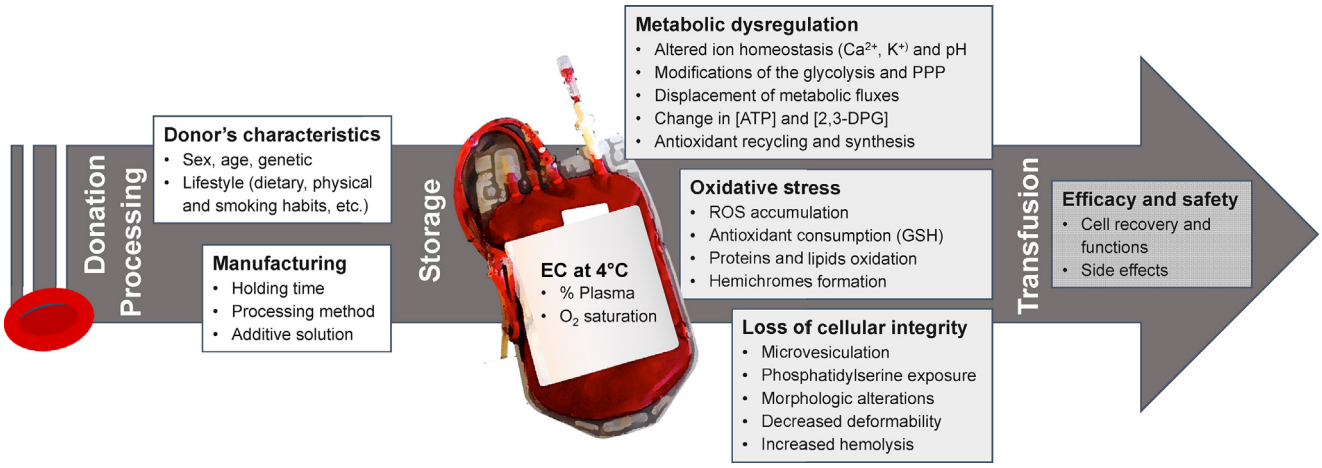

Fig. 1. The ex vivo journey of a red blood cell (RBC) for transfusion. The erythrocyte concentrate (EC) characteristics are dependent on the donor's characteristics and the manufacturing processes. During storage, the RBCs progressively accumulate storage lesions that can impair cell recovery when a transfusion is carried out, with possible deleterious side effects for the patient.

the transfusion and possibly being associated with deleterious side effects [10].

2. Fighting against oxidative stress

RBCs are well equipped to fight against oxidative stress because they are continuously in contact with oxygen, inherently to their carrier function. Under blood banking conditions, the exposure to oxygen is also strong, as recently reported by Yoshida et al. [11]. The authors demonstrated that the oxygen saturation in the ECs reaches 95–100% in three weeks. RBCs possess powerful enzymatic (e.g. peroxiredoxin-2, catalase, superoxide dismutase and glutathione peroxidase), and non-enzymatic (e.g. glutathione, vitamin C and E, and urate) antioxidant defenses to manage the continuous production of reactive oxygen species (ROS) (superoxide anion [$O_2^{\cdot -}$], hydroxyl radical [$^{\cdot}OH$], hydrogen peroxide [H_2O_2], etc.) [12]. Nevertheless, oxidative lesions accumulate at the level of the RBC proteins and lipids during storage [4–8], as a result of an imbalance between oxidants and antioxidants. One of the protective mechanisms of the RBCs is the degradation of ubiquitinylated proteins by the proteasome. However, this defense system might be altered after 4 weeks of storage [5]. The reason for this is probably the recruitment of damaged proteins at the membrane, as well as the inhibition of the proteasome by over-oxidized proteins. Other chaperone proteins, such as the heat shock proteins associate with misfolded or aggregated proteins participating in the response to oxidative stress [13]. Ultimately, the process of elimination by microvesiculation of the carbonylated proteins (an irreversible post-translational modification), takes over [5,8].

3. Evolution of the antioxidant power from donation to transfusion

After the donation, whole blood collected in anticoagulant is processed to separate the plasma, the RBCs, the leucocytes and the platelets. Each component is then stored individually under specific conditions. The preparation procedure and the modification of their extracellular environment have an effect on the RBCs. In vivo, RBCs, in common with all other cell types, are in a dynamic equilibrium with the environment. Immediately after donation this steady state is probably partially maintained as long as the cells remain in whole blood (i.e. 100% plasma). After blood processing, however, RBCs face completely new conditions: lower temperature, different pH, with only residual plasma diluted in the additive solution. In this context, it is likely that some molecules will be passively or actively exchanged between the intra- and the extracellular spaces. An example of such a balanced mechanism is the export of urate during the first week of storage, which could potentially result both in a metabolic shift and a reduction in the intracellular antioxidant pool [14]. The evolution of the extracellular antioxidant power (AOP) level was shown to be closely correlated to the urate concentration, which is the major antioxidant in plasma (120–450 μM) [15]. Similarly to the urate, the extracellular AOP did not follow a linear decrease but tended instead to increase during the first week of storage before decreasing until it reached a plateau value stable up to expiration date.

4. Variability in the red blood cells storage capacity

The variability in the RBC storage lesions observed between research teams, and even within a single group, cannot be explained solely by the analytical approach used to measure them, but can depend on several parameters. Firstly, one should remember that not just one kind of additive solution is used worldwide, but different types with diverse formulations, pH and osmolarity that may impact RBCs differently [16]. Secondly, the manufacturing parameters, such as the holding time between the whole blood donation and the blood component separation, the processing method (whole-blood or buffy-coat) and the type of commercial kit used, certainly have an effect on the final EC characteristics [17]. Finally, there is the fact that blood is a biological product derived from female and male donors, having different ages and blood groups, who are

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