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Perspective

The Advances in Producing and Preserving Red Blood Cells for Transfusion

Lou Chen*

Department of Biology and Education, Henan University, Kaifeng, China

DESCRIPTION

In animals, including humans, Red Blood Cells (RBCs) are the most prevalent type of cell. They serve a vital function of transporting oxygen and carbon dioxide throughout the body. RBCs are also being recognized more and more as biomarkers for a wide range of pathophysiological conditions, from those that are primarily associated with RBCs, like hereditary and acquired anaemias, to those that are not, like inflammatory conditions, cancer, diabetes, and cardiovascular issues.

The global demand for blood for transfusion applications is rising due to the aging population, increased surgical procedures, and emerging infectious diseases. However, the supply of blood from donors is limited and faces challenges such as blood type compatibility, risk of transmission of pathogens, and storage lesions. Therefore, there is a need for alternative sources of RBCs that can overcome these limitations and provide safe and sufficient blood products for transfusion.

One promising approach is the *in vitro* generation of RBCs from stem cells. Stem cells are undifferentiated cells that can give rise to various cell types through a process called differentiation. There are two main types of stem cells that can be used for RBC production: Hematopoietic Stem Cells (HSCs) and induced Pluripotent Stem Cells (iPSCs). HSCs are the natural source of RBCs in the body and can be derived from cord blood, adult bone marrow or peripheral blood. iPSCs are reprogrammed cells that can be derived from any somatic cell type and have the potential to differentiate into any cell type, including RBCs.

Both HSCs and iPSCs have advantages and disadvantages for RBC generation. HSCs have a proven track record of clinical application and can produce mature and functional RBCs. However, they have limited availability, variability in quality and quantity, and ethical issues associated with their collection. iPSCs have unlimited proliferative capacity, genetic stability, and potential to generate universal donor RBCs. However, they also have challenges such as low efficiency of reprogramming and differentiation, risk of tumorigenicity, and regulatory hurdles.

Several studies have reported the successful generation of RBCs from both HSCs and iPSCs using various protocols involving different culture conditions, growth factors, and genetic manipulations. However, there are still several challenges to overcome before these methods can be translated into clinical applications. Some of these challenges include scaling up the production process to meet the clinical demand, ensuring the quality and safety of the RBC products, optimizing the storage and preservation methods to maintain the viability and functionality of the RBCs, and evaluating the efficacy and immunogenicity of the RBCs in animal models and human trials.

In recent years, there have been some significant advances in addressing these challenges. For example, a new method to generate large quantities of RBCs from iPSCs using a three-stage culture system involving feeder cells, serum-free medium, and erythroid differentiation factors was reported by Oh et al. The method produced up to 10-12 RBCs per liter of culture volume with high purity and enucleation efficiency. The RBCs also expressed normal markers and functions such as hemoglobin synthesis, oxygen transport, and deformability.

Another example is a new protocol to preserve RBCs derived from HSCs or iPSCs using a synthetic oxygen carrier called ErythroMer. The protocol involved dehydrating the RBCs using a lyophilizer and rehydrating them with ErythroMer solution. The protocol resulted in improved survival and functionality of the RBCs after storage for up to four months at room temperature compared to conventional methods using refrigeration or freezing.

These advances suggest that *in vitro* generation of RBCs for transfusion medicine is moving from being a physics problem to an engineering one. However, more research is needed to optimize the production and preservation methods, as well as to validate the safety and efficacy of the RBC products in preclinical and clinical settings. The ultimate goal is to provide a reliable source of RBCs that can circumvent the shortfalls in global demand for blood for transfusion applications.

Correspondence to: Lou Chen, Department of Biology and Education, Henan University, Kaifeng, China, E-mail: louchen@ac.cn

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