REVIEW ARTICLE

Production of Hematopoietic Cells From Umbilical Cord Blood Stem Cells for Transfusion Purposes: Focus on *Ex Vivo* Generation of Red Blood Cells

ABSTRACT

Cord blood contains a heterogeneous population of stem cells and progenitors and, in addition to transplantation these cells could be used also for ex vivo production of mature cells, as red blood cells (RBC). The experimental ex vivo production of RBC, first demonstrated with cord blood CD34+ cells as a "raw material", is today a reality. The proof of principle for transfusion of ex-vivo-generated erythrocytes was provided recently. In this purpose, the CD34+ cells of other sources could be used: bone marrow, peripheral blood in steady state and after "mobilization" treatment, but also embryonic stem cells and adult Induced Pluripotent Stem Cells – iPSC. It is imperious today to decide which cell population will be used to produce ex-vivo erythrocytes for clinical applications. In addition, the culture system should be optimized with respect to physical parameters (for example oxygenation), up-scaling to the clinical grade and transferred to industrial level.

KEY WORDS

Umbilical cord, stem cells, red blood cells, transfusion of generated red blood cells.

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Cell engineering for cell therapy and transfusion

Traditional transfusion is based on injection in circulation of « labile hemoproducts » which, apart plasma, represent concentrates of mature blood cells. Thus, injection of the cells (mainly Red Blood Cells (RBC) and platelets) is aimed to replace temporarily their lack in circulation. The point is that transfusion is operating with the cells having definitive life span i.e. the cells which are not going to replicate and reconstitute in vivo a cell lineage or a tissue. On the contrary, cell therapy is based on injection of stem and progenitor cells i.e. the cells which should produce for short- or long-term, a cell offspring, hence, ensure a sustained production of mature cells belonging to one or more cell lineages.

The future of cell therapy is closely related to development of ex vivo technology for transformation and amplification of cells. Cell engineering should allow improving the grafts

based on stem cells and progenitors that already became reality in field of hematology, cardiology, endocrinology....¹

But cell engineering could also enable ex vivo production of mature cells for transfusion purposes, starting from CD34+ cells isolated from bone marrow, cord blood, or mobilized to peripheral blood; it is possible to produce megakaryocyte, granulocyte, as well as RBC. In this review, we are going to discuss some points related to ex vivo red blood cells generation from cord blood CD34+ cells.

CD34+ cells as a source of stem cells

Bone marrow, cord and peripheral blood cells expressing CD34 antigen are extremely heterogeneous cell population from a functional point of view. The idea that the expression of CD34 antigen is related to hematopoietic stem cells

has been a permanent source of misunderstanding and confusion (reviewed in ²). It should therefore be stressed that the fact the majority of hematopoietic stem and progenitors cells express CD34, does not mean that all CD34+ cells are stem cells or progenitors. In CD34+ population of cord blood, 30 to 50 % of cells are progenitors (CFU-GM, BFU-E, CFU mix and CFU Mk) and only a small percentage is a subpopulation of primitive stem cells. Approximately one half of CD34+ cell population does not exhibit either progenitor or stem cells functional properties. Furthermore, the situation is even more complicated: some stem cells do not express CD34 in steady state,³ and expression of this molecule could be reversible,⁴ and is not related to functional capacities of stem cells.

However, from a practical viewpoint, due to well developed and easily available technology for isolation of CD34+ cells, this cell population, relatively enriched in progenitor and stem cells represents a good starting point to ex vivo production of mature cells.

Cord blood CD34+ cells

CD34+ population from cord blood is composed of progenitors and stem cells exhibiting a higher proliferative capacity than those in CD34 cell population isolated from adult bone marrow and peripheral blood.⁵ In fact, cord blood is nothing else than neonatal blood, i.e. its part remaining in placenta after the umbilical cord is cut. These high proliferative capacities of stem and progenitor cells from cord blood seem to be attractive for ex vivo production of mature cells, since enabling a good yield. In addition, the sampling of cord blood is neither harmful for the mother nor for the baby nor related to serious ethical issues as some other sources of stem cells (embryonic stem cells). On the other hand, the need for cord blood cells in transplantation purposes could appear as a limiting factor for their use for ex vivo generation of mature cells. In fact, this problem could be easily solved by choosing only cord blood units rejected from the bank due to a cell number/volume lower than the bank standards. For all these reasons, CD34+ cells isolated from cord blood were and are regularly used in experiments aimed to enable a production of mature cells ex vivo.

Ex vivo production of RBC from stems cells: a need in transfusion medicine

Fulfilling the worldwide need for 96 million red cells transfusion per year meets several limitations.²¹ First problem comes from demographic evolution which predicts important increase of world population aging in the coming decades (e.g. percentage of persons over 60, will

reach 32% in 2050 in France). This will increase considerably the number of malignant haematological conditions which have important requirement for RBC transfusion.²² On the other hand, the numbers of blood donors will raise much more slowly. Secondly, even in developed transfusion system, the risk of transfusion transmitted infection (TTI) can be really high due to elevated prevalence of the infectious disease spreading world widely and not adequate blood testing infrastructure.²¹ Therefore, finding the alternatives to conventional transfusion practice as it is transfusion of ex vivo generated RBC, may become unavoidable future. In addition, development of strategies for ex vivo production of RBC offers the possibility to generate RBC expressing patient's specific blood group antigens or even "universal" RBC lacking membrane expression of two principal blood group systems, ABO and RHD. This might resolve the problem of the alloimmunisation in the frequently transfused patients (patients with thalassemia major and sickle cell disease) or transfusion of patients with rare blood phenotype. Finally, ex vivo produced RBC could be used as control samples for the immunehematologic testing and screening of RBC alloantibodies in patients who received multiple transfusions.

RBC from CD34+ cells

Appearance of colonies composed of hemoglobinized cells in semi-solid medium indicates in vitro erythroid differentiation from progenitor to precursor state.⁶ These cultures in semi-solid medium are still in use to enumerate erythroid progenitors in a cell population. Their efficiency is highly improved with combination of cytokines and growth factors allowing/stimulating differentiation of erythroid progenitors. The "red" colonies (CFU-E, BFU-E) are composed mainly of erythroid precursors (starting from pro-erythroblasts), but in these cultures, the final erythroid maturation does not occur. This methodology didn't enable the production of homogene population of erythroid cell types produced which can be easily isolated and analyzed. This problem was technically accomplished by development of two phase liquid culture ex vivo models of erythropoiesis, proposed by Fibach et al (24) and modified after by several groups (24-28). Briefly, In the first, erythropoietin-independant phase peripheral blood mononuclear cells or CD34+ derived from different origin (bone marrow, cord blood, peripheral blood) were cultivated in presence of different combination of the growth factors (originally, in presence of the conditioned medium from human bladder carcinoma). This phase allows generation of primitive erythroid progenitors BFU-E which proliferate and differentiate in more mature CFU-E. In second, EPO-dependant phase, presence of EPO in combination with other synergistic cytokines, allows generation of erythroid precursors with high yields of orthochromatic normoblasts and minority of enucleated erythrocytes. Just

for the illustration, we can mention that using this model Freyssinier et al obtained CD36⁺ population of erythroid progenitors by cultivated CD34⁺ derived cord blood and mobilised peripheral blood in serum-free condition with SCF, IL-3, IL-6, in the first phase culture. These cells developed in erythroid precursors in the secondary culture in presence of EPO. Production overview was that from 10^6 CD34⁺ cells input this model enabled generation of 10^7 CD36⁺ cells at Day 7 and of 1.5×10^8 precursors after 3 days of secondary culture (100-fold expansion).²⁶

It should be mentioned that the others managed to reach terminal erythroid maturation using mono-phase culture system. For example Malik et al, showed that in presence of IL-3, GM-CSF, and high concentration of EPO, ex vivo production of erythroid precursors from CD34⁺ from bone marrow, cord blood, and peripheral blood, was supplemented with ten to forty percentage of the enucleated erythrocytes showing the characteristics of reticulocytes and expressing γ -globin and β -globin depending of the source.²⁹

More efficient and sophisticated era of the ex vivo RBC production started when professor Douay's group published its first paper explaining how to get a massive amplification of a pure erythroid precursor population by applying a sequential specific combination of growth factors during the culture, designed first to amplify hematopoietic stem cells, to differentiate them to erythroid progenitors, and then to induce their terminal differentiation.⁷ This approach used a three-phase culture. In the first phase, aimed to differentiate committed progenitors till precursor stage from CD34⁺ cord blood cells, was a classical liquid culture supplemented by FLT-3 ligand (FLT-3L) stem cell factor (SCF) and thrombopoietin (TPO). After this week long phase, the cells were resuspended in medium containing SCF insulin growth factor (IGF) and erythropoietin (EPO) for further 7 days. Finally, the cells were washed and resuspended in medium with EPO only.

Although not ideal, this procedure showed that a massive and exclusive production of erythroid precursors (up to 99%) containing fetal hemoglobin (amplification up to 200000 times) is possible ex vivo. Since in cord blood, RBC fetal hemoglobin is a major component, the proportion fetal/adult hemoglobin decreased after culture but not reaching the proportion in adult RBC, where adult hemoglobin is predominant. Even if reticulocytes were only occasionally present in culture endpoint cell population (all stages from pro-erythroblasts to ortho-chromatic erythroblasts were present), these ex vivo generated erythroid cells injected in non-obese diabetic/severe combined immunodeficient (NOD/Scid) mice continued with terminal maturation and gave enucleated RBCs in vivo producing adult hemoglobin.⁷ The fact that the complete terminal differentiation is accomplished only in vivo, pointed to a crucial role of erythropoietic microenvironment for the full

maturation of RBC. That's why, few years later, the same group improved the system by combining a liquid culture with a co-culture with stromal cells.⁸ Starting from cord blood, bone marrow or peripheral blood CD34⁺ cells the first culture phase (8 days) was stimulated by interleukin-3 (IL-3), SCF, EPO in presence of hydrocortisone. The cells were then transferred to a stromal layer (murine stromal cell line MS5 or adult human bone marrow obtained from healthy donors) in presence of EPO only for next 3 days and then washed and reseeded on adherent layer in medium without growth factors.⁸

These modifications resulted in virtually pure population (90-100%) of enucleated cells, mainly composed of reticulocytes. These ex vivo generated erythrocytes display characteristics close to those of native ones (volume and hemoglobin content). Interestingly, in contrast to bone marrow or peripheral blood CD34⁺, ex vivo generated RBC from cord blood CD34⁺ cells contained mostly fetal hemoglobin. In these conditions, the expansion reached amazing 10^6 - 10^7 fold with respect to the starting number of CD34⁺ cord blood cells.⁸

After being injected into circulation of NOD/SCID mice, these ex vivo produced reticulocytes mature up to final RBC. These cells show normal enzyme expression, membrane deformability and oxygen dissociation characteristic similar to those of native erythrocytes.

Ex vivo RBC production yield

If one would like to utilize ex vivo generated RBC for purpose of transfusion, the number of produced cells should correspond to one presented in the unit of conventional RBC "concentrate" which contains approximately 2000 billions of cells (2000×10^9). To accomplish this challenge, the best choice of the starting material, according to our and others' experience,²² is cord blood CD34⁺ cells. Their proliferative capacity is 5 to 10 times higher than those of peripheral blood CD34⁺ cells.

Ex vivo systems enabled to produce 4 to 22 millions of RBC from one cord blood CD34⁺ cell. Knowing that average cord blood donation contains from 2 to 5 million of CD34⁺ cells, we can easily calculate that from only one cord blood unit equivalent of the 10 to 50 RBC units can be produced.

Improving the system

These results have been confirmed by other groups,^{9,10} including ours.¹¹ In attempt to improve the system according to our "Oxygen Stem Cell Paradigm",¹² we hypothesized that the yield of RBC could be further improved

Figure 1. Oxygen gradient in bone marrow.

by adapting the oxygenation of each stage of culture to physiologic one. It is known that erythropoiesis takes on in micro-environment of bone marrow niches exposed to relatively low O₂ concentrations (from almost 0 near the endosteum to 8 % at the edge of blood vessels).¹³⁻¹⁶ In the course of their proliferation, differentiation and maturation, erythroid cells migrate towards the longitudinal access of bone marrow, reaching more oxygenated areas as they approach blood circulation (Figure 1). Also, some literature data obtained with cord blood cells strictly suggested that at 1% O₂, the production and amplification of BFU-E (EPO-independent cells) seemed to be enhanced, while their commitment toward CFU-E and further is accomplished at higher O₂ concentrations.¹⁷

Thus, we extended our “Oxygen Stem Cell Paradigm” to erythroid progenitors,¹² and hypothesized that the sequential establishment of an optimal O₂ concentration for each development stage of hematopoiesis/erythropoiesis enhanced the amplification of primitive stem cells and erythroid progenitors as well as the proliferation of the latter, and consequently, boosted RBC production. So, adapting the early phase of erythropoiesis to physiologically low oxygenation (1.5 to 5%) (Figure 2), we increased by several fold the amplification of primitive erythroid progenitors before inducing latter steps of erythropoiesis. An additional advantage was obtained during the phase 2 and 3 of culture (erythroid maturation and nucleus expulsion) if the culture was exposed to 13% O₂ concentration with respect to that of air (20-21%) (Figure 2). Thus, just by approaching culture oxygenation conditions to the physiological one, we realized 2 to 3 fold higher yield of mature enucleated RBCs (morphology at each culture point, Figure 3).¹¹

The other interesting proposition came from Fujimi et al, who cultivated CD34+ cord blood cells on a telomerase gene

Figure 2. Culture designed to mimic the bone marrow oxygen gradient.

Figure 3. Morphology of erythroid cells at different culture time-points and with respect to oxygenation level.

transduced (hTERT) human stromal cell line, followed by the simple culture phase, succeeded by the co-culture with macrophages derived from parallel co-culture of CD34+ cells on hTERT stromal cells in presence of macrophage colony stimulating factor (M-CSF) and granulocyte colony stimulating factor (G-CSF). But this costly system didn't overcome the degree of enucleation in the final phase and the expansion rate obtained in previous protocols.^{8,23}

Simplification of the procedure

In order to simplify the procedure for the ex vivo RBC production interesting proposal came from Miharada et al, who developed a stroma-free protocol. Using cord blood CD34+ cells in liquid culture in presence of VEGF,

IGF-2, mifepristone, antagonist of glucocorticoid function and human serum, they were capable of generating 4×10^{12} erythroid cells from a single donation of around 5×10^6 CD34+ cells (700,000 fold expansion).³⁰ They demonstrated that contact with stromal cells is not absolutely necessary for the enucleation since it was not completely abrogated by elimination of contact between MS-5 cells and erythroid cells. According to the obtained results, authors concluded that: the interaction of erythroblasts with other cells is not necessary and that signals mediated by humoral factors seem to be sufficient for efficient autonomous completion of erythroblast enucleation.

But, this system was not as efficient as previous ones:⁸ it enabled terminal differentiation where the percentage of enucleated cells was 77.5% compared with 98% reported by Giarratana et al.⁸

Proof of principle for transfusion of in vitro generated RBCs

All these data were obtained in experimental conditions in small culture systems allowing production of RBC volumes sufficient only to confirm the principle. Professor Douay's group produced milliliter-range quantities of RBCs from peripheral blood CD34+ cells).¹⁸ Peripheral blood CD34+ obtained by leukapheresis after mobilization with G-CSF were expanded by using three-step protocol previously described by the same group; but in this work stromal cells were replaced by detergent virus-inactivated human plasma, which was sufficient to accomplish erythroid differentiation and enucleation (68%) Immunophenotypic characterization of enucleated cells confirmed their reticulocytes profile. These cells synthesized mostly adult Hb and showed enzyme content, deformability and Hb functionally corresponding to those of native RBC. Blood group antigens expression from ex vivo generated RBC and native RBC from the same donor didn't show notable difference.

Homogeneous sample of 10^{10} Day 18 reticulocytes generated under good manufacturing practice conditions and labeled with ⁵¹Cr were re-injected to the same donor (autologous context).¹⁸ The level of these cells in the circulation 26 days after injection was between 40-60% which is comparable with reported half-life of approximately 28 days for the native RBC.

This work demonstrated a normal behavior and functional properties of ex vivo generated RBCs. This is the first proof of principle for transfusion of in vitro generated RBCs. Although similar assay was not done with RBCs ex vivo generated from cord blood CD34 cells, we could suppose with reasonable probability that it would yield similar results.

Conclusion and perspectives

Experimental RBCs ex vivo production from cord blood CD34+ cells turned out to be feasible. Ex vivo generated RBCs exhibit similar properties as "natural" RBCs. Although not done with RBCs generated from cord blood CD34+ cells, a proof of principle for transfusion of ex vivo generated RBCs is provided. The challenge now is to develop a large-scale procedure allowing to get clinically relevant RBCs quantities that should be compatible with industrial production.¹⁹ Of course, red cell concentrates produced this way should be tested to demonstrate their efficiency that will require clinical trial with very large number of patients.

However, there is a conceptual dilemma raising a question which should be addressed before launching such an expansive enterprise: from where to start,²⁰ i.e. which cell population use as raw material for RBC production. It seems that the traditional source of CD34+ cells as bone marrow, blood or umbilical cord are less attractive today than the pluripotent embryonic stem cells or adult Induced Pluripotent Stem Cells (iPSC).^{20,21}

Very complicated matter is the blood type phenotype. With that respect also, iPSC seem to provide an advantage. It is estimated that 3 different cell lines, could enable the RBC offspring "covering" 99% of erythrocyte phenotype needed for Caucasian population.²⁰

Whatever choice of starting cell population, RBC production will surely be costly, at least at the beginning, before establishing a large-series industrial process. While initially, when adult and CD34+ cells were primarily considered, it was supposed that ex vivo production of RBCs could be particularly useful to produce RBCs of rare blood type phenotypes, these new possibilities with iPSC bring a hope to "cover" all patients. The industrial-scale RBC production, which depends on the amount of investment, probably would not start in 5 to 10 years.

Authorship statement

Both authors contributed equally.

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Perspektiva korištenja hematopoetskih ćelija iz krvi pupčane vrpce (placentarne krvi) u transfuziji: fokus na stvaranje eritrocita *ex vivo*

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APSTRAKT

Krv iz pupčane vrpce (placentarna krv) sadrži populaciju matičnih ćelija i progenitora opredeljenih za ćelije pojedinih krvni loza. Te ćelije mogu se koristiti u svrhu transplatacije, ali i za proizvodnju zrelih ćelija - poput eritrocita. Eksperimentalna proizvodnja eritrocita *ex vivo* pomoću CD34+ ćelija je ostvarena pre jedne decenije. Odnedavno postoji dokaz da se tako stvoreni eritrociti mogu koristiti u transfuziji. Matične ćelije i progenitori iz drugih izvora (kostna srž, periferna krv) kao i embrionalne matične ćelije i pluripotentne matične ćelije indukovane iz zrelih ćelija mogu se takođe koristiti za proizvodnju eritrocita za transfuziju.

KLJUČNE RIJEČI

Placentarna krv, matične ćelije, eritrociti, transfuzija proizvedenih eritrocita.