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Discarded leukoreduction filters: A new source of stem cells for research, cell engineering and therapy?

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Abstract New adult stem cell sources, devoid of the technical/ethical/economical barriers of those presently available, would favor the ongoing development of in vitro cell engineering and transplantation.
Hematopoietic transplantation opened the way to and remains the most successful cell transplantation procedure. CD34+ cells that include hematopoietic stem cells (HSCs) and hematopoietic progenitors (HPs) are presently harvested from bone marrow (BM), cord blood or peripheral blood (after being mobilized from BM). The panel of potential donors, the quantities of collected cells and some other technical/medical problems still represent limiting factors to their transplantation in some patients. Steady state peripheral blood (SSPB) contains very low frequencies of CD34+ cells. They are trapped in leukoreduction filters (LRFs), which are discarded after the preparation of therapeutic red blood cell concentrates from individual blood donations. We recently developed a procedure allowing the easy and rapid elution of CD34+ cells from LRFs and we showed that they are functionally similar to those harvested from other sources.
After providing an overview of the sources, interests and limitations of therapeutic HSCs presently available, we will provide arguments based on our and others' results suggesting that SSPB could become an attractive source of HSCs for hematopoietic transplantation and of other cell types for various research/development procedures.

Contents

Abbreviations: BM, bone marrow; CB, umbilical cord blood; G-CSF, granulocyte colony stimulating factor; HPs, hematopoietic progenitors; HSCs, hematopoietic stem cells; iPS cells, induced pluripotent stem cells; LRFs, leukoreduction filters; PB, peripheral blood; RBCs, red blood cells; SSPB, steady state peripheral blood; WBCs, white blood cells.

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Introduction

Transplantation of autologous or allogeneic hematopoietic stem cells (HSCs) dramatically improved the disease free survival of numerous patients with hematological diseases and presently remains the only widely used cellular transplantation procedure (Deeg and Bartenstein, 2011; Gladstone and Fuchs, 2012). Bone marrow (BM) HSCs are characterized by their life-long capacities to either remain quiescent or proliferate and to either self-renew or differentiate (Lerner and Harrison, 1990; Bradford et al., 1997). These tightly regulated balances allow the life-long homeostatic production of mature functional blood cells, as well as the adaptation/reconstitution of hematopoiesis after infection, hemorrhage or myeloablative stress. During the last 40 years the continuous improvement of our knowledge about hematopoiesis and the development of suitable in vitro techniques for the large-scale isolation, maintenance and expansion of HSCs have increased the numbers and indications of hematopoietic transplantations. They have reduced in parallel the duration of the post-transplantation cytopenia and its related morbidity/mortality consequences.

In 1984, the identification of the CD34 glycoprotein as a marker of HSCs and of hematopoietic progenitors (HPs) (Civin et al., 1984) opened the way to their isolation from BM, umbilical cord blood (CB) and blood mobilized CD34+ cells and to the development of transplantation with in vitro expanded cells. However medical, economical and/or technical constraints still limit their therapeutic use in some patients and/or countries. The main purpose of this brief review is to discuss the potential interest of steady state peripheral blood (SSPB) CD34+ cells trapped in leukoreduction filters (LRFs), which are discarded after the preparation of therapeutic red blood cell (RBC) concentrates, as a new alternative source of HSCs for research and hematopoietic transplantation. We will also mention and discuss briefly some other possible uses for the CD34+ cells and other cell types eluted from these LRFs.

Current therapeutic HSC sources: interests and limitations

Bone marrow

About 50 years ago, successful human hematopoietic transplantations confirmed that transfusion of a limited number of HSCs and HPs collected from human BM was able to give rise to the rapid short-term (HPs) and long-term (HSCs) reconstitution of all hematopoietic lineages in patients (Mathe et al., 1959; Thomas, 1999). However, obtaining BM derived HSCs for therapy faces several technical and/or economical difficulties: i) it is an invasive procedure performed under general anesthesia, thus leading to a very low but real morbidity/mortality risk that cannot be ignored for allogeneic healthy BM donors (Pamphilon et al., 2009); ii) due to the very low percentage of CD34+ cells, an important volume of BM (500 to 1500 mL) must be collected and then processed through a multistep procedure to eliminate maturing granulocytes, platelets and RBCs. Collecting this large volume of BM induces a moderate but real donor RBC depletion that has also to be considered; and iii) the socio-economical impact of a BM donation is costly if one considers that it requires a brief hospitalization and a limited period of restricted activity. The appearance of non-invasive and easy alternative sources of HSCs in numbers sufficient for adults' engraftment reduced the transplantation of BM cells to about 20%.

Mobilized adult blood HSCs

Mobilization of HSCs and HPs from their specific BM niches to the peripheral blood (PB) after chemotherapy was first described in 1976 (Richman et al., 1976). It rapidly led to the development of cell therapy procedures that used the capacity of various chemotherapeutic agents and of some growth factors (granulocyte colony stimulating factor [G-CSF] mostly) to induce the BM to blood egress of numerous CD34+ cells (Siena et al., 1989), containing HSCs and primitive HPs (To et al., 1984; Körbling et al., 1986; Sato et al., 1994). Three major reasons explain that blood mobilized CD34+ cells are now the major source of therapeutic HSCs: i) the good security and tolerance of the G-CSF conditioning processes; ii) the rapid, complete and long term hematopoietic recovery provided by blood mobilized HSCs; and iii) the technical improvements of cytapheresis materials and procedures. However, the drug/growth factor "mobilization process" has also some side effects (bone pain, fatigue, changes in blood cells ratios) that must be taken into consideration, especially for healthy donors (Bosi and Bartolozzi, 2010). In addition, mobilization is inefficient in a low percentage of "poor mobilizers" (Benboubker et al., 2001; To et al., 2011). Despite these limitations, transplantation of blood mobilized CD34+ cells progressively became the standard procedure for auto- and allo-graft (To et al., 2011; Körbling and Freireich, 2011) since it largely improved the benefit/risk ratio for both the