ELSEVIER

editorial

Philippe Taupin

Ex vivo fucosylation to improve the engraftment capability and therapeutic potential of human cord blood stem cells

Hematopoietic stem cells (HSCs) are the self-renewing multipotent cells that give rise to the differentiated phenotypes of the blood and immune systems. The transplantation of HSCs is used to treat patients with malignant and non-malignant hematologic diseases, like leukemia, lymphoma, myeloma, Fanconi anemia and sickle cell anemia [1]. In adults, the bone marrow (BM) is the primary source of HSCs. The limited access of HSCs of the BM is the main obstacle for their use in therapy. The umbilical cord blood (CB) contains three to six times more repopulating HSCs than the BM or mobilized peripheral blood [2]. It offers an alternative source of tissue for the transplantation of HSCs, with ease of access and higher potential to reconstitute the BM [3,4].

Since the first successful transplantation of CB stem cells in children with Fanconi anemia – a rare genetic disease characterized by genomic instability and BM failure –, CB tissues have been widely used not only for pediatric transplants, but also for transplantations in adults [5,6]. The main limitations with the use of CB tissues for HSC transplantation are the low cell dose available, the delayed and poor engraftment of the CB stem cells to the BM [7]. Several strategies are being considered and proposed to overcome these issues: the transplantation of double dose or unit of CB and the propagation of CB stem cells *in vitro*, to generate higher number of cells for grafting. The transplantation of double dose of CB is currently proposed for therapy, particularly in adults [8]. On the one hand, the transplantation of double dose of CB does not resolve the efficiency of the therapeutic transplantation and limits the availability of CB tissues for treating patients. On the other hand, the propagation of CB stem cells *in vitro* carries the risk of altering the developmental and therapeutic potential of the cells and optimal culture conditions remain to be established [9]. In adults, the mortality rate of patients treated with CB stem cells for HSC transplantation remains high [10]. Further improvements in engraftment are mandated to achieve higher rate of success for CB transplantation and alternative strategies must be sought.

HSCs migrate to their niches in the BM, a process known as homing, from where they give rise to the differentiated lineages of the blood and immune systems. During homing, the HSCs migrate through the blood and across the endothelial vasculature to reach their niches, particularly in the BM [11]. HSCs have been identified and characterized as a population of cells enriched in $CD34^+$ $CD38^{-/low}$ or $CD34^+$ cells. The rolling and migration of HSCs on endothelial cells involve complex molecular and cellular interactions. Among them, is the interaction between the P- and E-selectins and their ligands, the selectin glycoprotein ligands

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2010.05.006

(SGLs). P- and E-selectins are expressed constitutively on endothelial cells, whereas SGLs are expressed on $CD34^+$ HSCs of the BM and CB in mice and in humans. The interaction P- and E-selectins on endothelial cells with SGLs on HSCs underlies the rolling and migration of HSCs to the BM [12]. HSCs isolated from human BM, but not from CB, migrate efficiently to the BM when transplanted in irradiated non-obese diabetic/severe combined immune deficiency mice [13]. The failure of CB HSCs to migrate efficiently to the BM is due to a defect in binding of P- and E-selectin to the SGLs on their surface. Hence, human CB HSCs express a form of SGL that does not bind to P- and E-selectin and as a result elicit poor homing capabilities, in contrast to their BM counterpart.

SGLs display a glycan determinant on their N-terminal region, a sialylated Lewis x (sLex). The sLex determinant, on the N-terminal region, of SGLs of human BM HSCs, but not of CB HSCs, carries a α2–3-linked sialic acid and a α1–3-linked fucose component [14]. The lack of α1–3-fucosylation of the sLex determinant of CB HSCs causes defective binding of P-selectin and E-selectin to SGLs [15,16]. Hence, proper sLex determinant on the surface of HSCs, a post-translational event, underlies their binding to P-selectin and E-selectin on endothelial cells and their homing capability to the BM. *Ex vivo* membrane fucosylation of CB CD34+ HSCs, by α1–3-fucosyltransferase VI, augments the homing to and engraftment of the cells to the BM in rodents [17]. α1–3-fucosylation of sLex would enhance the binding capabilities of P- and E-selectin to SGLs of CB HSCs and the efficiency of their migration and homing to the BM, through the interaction of P- and E-selectin with SGLs.

Homing is an important step in transplantation therapies involving HSCs [11]. CB transplantation has a tremendous potential for treating hematologic and BM diseases. However, it is limited by the low cell dose in CB tissues, the delayed and poor engraftment of CB stem cells to the BM. Strategies aiming at improving the engraftment of CB stem cells to the BM may overcome these limitations. It would improve the homing of CB stem cells to the BM, reduce the delayed engraftment of the cells and improve the success of therapy with lower cell doses, reducing the need for double CB dose for transplantation. This would result in higher efficiency of the therapeutic transplantation, particularly in adults, and more CB tissues available for patients. To this aim, *ex vivo* fucosylation of human CB stem cells' prior transplantation may provide an alternative and promising strategy for the transplantation of CB tissues. It may improve the engraftment capability of human CB stem cells to the BM and the therapeutic potential of CB tissues, particularly for adults.

References

1 Thomas, E.D. (1995) History, current results, and research in marrow transplantation. *Perspect. Biol. Med.* 38, 230–237
2 Wang, J.C. *et al.* (1997) Primitive human hematopoietic cells are enriched in cord blood compared with adult bone marrow or mobilized peripheral blood as measured by the quantitative in vivo SCID-repopulating cell assay. *Blood* 89, 3919–3924
3 Broxmeyer, H.E. *et al.* (1992) Growth characteristics and expansion of human umbilical cord blood and estimation of its potential for transplantation in adults. *Proc. Natl. Acad. Sci. U. S. A.* 89, 4109–4113
4 Kurtzberg, J. *et al.* (1996) Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. *N. Engl. J. Med.* 335, 157–166
5 Gluckman, E. *et al.* (1989) Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilicalcord blood from an HLA-identical sibling. *N. Engl. J. Med.* 321, 1174–1178
6 Ballen, K. (2010) Challenges in umbilical cord blood stem cell banking for stem cell reviews and reports. *Stem Cell Rev.* 6, 8–14
7 Barker, J.N. *et al.* (2003) Umbilical cord blood transplantation: current practice and future innovations. *Crit. Rev. Oncol. Hematol.* 48, 35–43
8 Kelly, S.S. *et al.* (2010) Overcoming the barriers to umbilical cord blood transplantation. *Cytotherapy* 12, 121–130
9 McNiece, I.K. *et al.* (2002) Ex vivo expanded cord blood cells provide rapid engraftment in fetal sheep but lack long-term engrafting potential. *Exp. Hematol.* 30, 612–616
10 Long, G.D. *et al.* (2003) Unrelated umbilical cord blood transplantation in adult patients. *Biol. Blood Marrow Transplant.* 9, 772–780
11 Lapidot, T. *et al.* (2005) How do stem cells find their way home? *Blood* 106, 1901–1910
12 Katayama, Y. *et al.* (2003) PSGL-1 participates in Eselectin-mediated progenitor homing to bone marrow: evidence for cooperation between Eselectin ligands and 4 integrin. *Blood* 102, 2060–2067
13 Hidalgo, A. *et al.* (2002) Functional selectin ligands mediating human CD34+ cell interactions with bone marrow endothelium are enhanced postnatally. *J. Clin. Invest.* 110, 559–569
14 McEver, R.P. (2002) Selectins: lectins that initiate cell adhesion under flow. *Curr. Opin. Cell. Biol.* 14, 581–586
15 Fuhlbrigge, R.C. *et al.* (1997) Cutaneous lymphocyte antigen is a specialized form of PSGL-1 expressed on skin-homing T cells. *Nature* 389, 978–981
16 Wagers, A.J. *et al.* (1998) Interleukin 12 and interleukin 4 control cell adhesion to endothelial selectins through opposite effects on 1,3-fucosyltransferase VII gene expression. *J. Exp. Med.* 188, 2225–2231
17 Xia, L. *et al.* (2004) Surface fucosylation of human cord blood cells augments binding to P-selectin and E-selectin and enhances engraftment in bone marrow. *Blood* 104, 3091–3096

Philippe Taupin
School of Biotechnology, Dublin City University, Glasnevin, Dublin 9, Ireland
email: philippe.taupin@dcu.ie