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Review

Umbilical Cord Blood: A Trustworthy Source of Multipotent Stem Cells for Regenerative Medicine

Tang-Her Jaing

Division of Hematology and Oncology, Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung University, Taoyuan, Taiwan

It is conservatively estimated that one in three individuals in the US might benefit from regenerative medicine therapy. However, the relation of embryonic stem cells (ESCs) to human blastocysts always stirs ethical, political, moral, and emotional debate over their use in research. Thus, for the reasonably foreseeable future, the march of regenerative medicine to the clinic will depend upon the development of non-ESC therapies. Current sources of non-ESCs easily available in large numbers can be found in the bone marrow, adipose tissue, and umbilical cord blood (UCB). UCB provides an immune-compatible source of stem cells for regenerative medicine. Owing to inconsistent results, it is certainly an important and clinically relevant question whether UCB will prove to be therapeutically effective. This review will show that UCB contains multiple populations of multipotent stem cells, capable of giving rise to hematopoietic, epithelial, endothelial, and neural tissues both in vitro and in vivo. Here we raise the possibility that due to unique immunological properties of both the stem cell and non-stem cell components of cord blood, it may be possible to utilize allogeneic cells for regenerative applications without needing to influence or compromise the recipient immune system.

Key words: Umbilical cord blood (UCB); Regenerative medicine; Multipotent stem cells; Mesenchymal stem cells (MSCs)

BACKGROUND

Cord blood cells have shown considerable utility for replacement of bone marrow transplants in a variety of clinical settings. The ethnic diversity, relative ease of collection, ready availability as cryopreserved units from cord blood banks, reduced incidence and severity of graft-versus-host disease (GVHD), and tolerance of higher degrees of human leukocyte antigen (HLA) disparity between donor and recipient are positive attributes when compared to bone marrow or cytokine-mobilized peripheral blood. Outside the area of oncology, the clinical use of umbilical cord blood (UCB) has expanded into various areas that range from reconstituting a defective immune system (16) to correcting congenital hematological abnormalities (12,13) through to inducing angiogenesis (30). The purpose of this article is to put forth the notion that the immunology of cord blood transplants for regenerative applications has to be viewed differently from the perspective and the practice of cord blood transplants for hematopoietic reconstitution.

THE HUMAN UMBILICAL CORD: A SOURCE OF STEM CELLS

UCB has been widely considered an important stem cell source because of its many pluses compared with other stem cell sources. Moreover, UCB is also viewed as a primary stem cell source due to the annual global human birth rate of more than 100 million a year. UCB is easily and safely collected by UCB banks and preserved as future therapeutic genetic material (1). UCB has been considered as a good alternative for embryonic stem cells lately, also because it has proved to contain populations of multipotent stem cells, which are able to differentiate into a variety of cell types, including epithelial, endothelial, myotubes, and neural (10).

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Address correspondence to Tang-Her Jaing, M.D., Division of Hematology and Oncology, Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung University, 5 Fu-Shin Street, Kwei-Shan, 333, Taoyuan, Taiwan, ROC. Tel: +886-3328-1200, ext. 8206; Fax: +886-3328-8957; E-mail: jaing001@cgmh.org.tw

REGENERATIVE CELLS IN CORD BLOOD

Numerous publications have described the regenerative ability of UCB cells in a myriad of preclinical disease models. In recent years, investigators have investigated the utility of cord blood for a variety of additional uses. These include treatment of neurological disorders, cardiac infarcts, as well as isolation of specific subtypes of cells from a cord blood sample. More recently, investigators have observed that cord blood is an excellent source of naive cells for making induced pluripotent cells. UCB contains mononuclear cells that are ~40% monocytes (macrophage precursors), ~40% lymphocytes, 10% neutrophils and other types of leukocytes, and the remaining 10% are stem cells and progenitor cells, including cluster of differentiation 34 positive ($CD34^+$) endothelial progenitor cells, $CD133^+$ multipotent stem cells, and $CD105^+$ mesenchymal stem cells (MSCs).

Hematopoietic Stem Cells

In contrast to marrow, $CD34^+$ cells from UCB possess higher proliferative potential in vitro (29). When transplanted in vivo, UCB has greater repopulating ability than bone marrow (BM) or mobilized peripheral blood (MPB). The potent hematopoietic activity of cord blood-derived $CD34^+$ cells may be attributed to the fact that cord blood is a much more developmentally immature source of stem cells as opposed to stem cells derived from adult sources.

Mesenchymal Stem Cells

MSCs are refined as multipotent, undifferentiated cells that can self-renew, regenerate mesenchymal tissues and blood cells, and differentiate into several cell types such as chondrocyte, adipocyte, osteocyte, osteoblast, myocyte, cardiomyocyte, neuron-like cell, as well as into insulin-producing cells (18,21). MSCs adhere to plastic and express a nonhematopoietic cell surface phenotype, consisting of not expressing CD34, CD45, and HLA-DR, while possessing markers such as stromal antigen (STRO-1), vascular cell adhesion molecule (VCAM), CD13, CD29, CD44, CD90, SH-2 (CD105 or endoglin), and SH-3 (3,8). Currently, this cell population is second to bone marrow stem cells in terms of clinical entry in that phase III clinical trials are already under way with these cells (24).

Endothelial Progenitors and Angiogenesis-Stimulating Cells

In addition to being a source of hematopoietic cells, cord blood contains potent angiogenesis-stimulating cells. Several phenotypes have been ascribed to cord blood angiogenic stimulating cells (2,23). In one report, the $CD34^+$, $CD11b^+$ fraction, which is approximately less than half of the $CD34^+$ fraction of cord blood, was demonstrated to possess the ability to differentiate into functional endothelial cells in vitro and in vivo (11).

MSC-Like Cells From Human Umbilical Cord Tissue: Roadmap to Clinical Research in Regenerative Therapies

Cumulatively, the identification and isolation of these populations of pluripotent stem cells within cord blood represents a scientific breakthrough that could potentially impact every field of medicine via their use in regenerative medicine. Fresh cord blood is rich in nonhematopoietic stem cells and also contains endothelial cells, MSCs, and unrestricted somatic stem cells (20). Thus, CB stem cells are amenable to treatment of a wide variety of diseases including cardiovascular, hepatic, ophthalmic, orthopedic, neurological, and endocrine diseases (6,7,9,31). Moreover, the presence of phenotypic and functional markers for dopaminergic neurons, oligodendrocytes, and astrocytes on differentiation demonstrates the full range of the cell's neural differentiation ability (25).

Ex Vivo Modulation Strategies to Enhance the Therapeutic Potential of Cord Blood

UCB contains an inherently limited hematopoietic stem cell (HSC) count, which is associated with delayed time to engraftment, high graft failure rates, and early mortality. 16,16-Dimethyl prostaglandin E2 (dmPGE2) was previously identified to be a critical regulator of HSC homeostasis, and it was hypothesized that a brief ex vivo modulation could improve patient outcomes by increasing the "effective dose" of HSC. North et al. showed that chemicals that enhance prostaglandin (PG) E2 synthesis increased HSC numbers, and those that block prostaglandin synthesis decreased stem cell numbers (22). The cyclooxygenases responsible for PGE2 synthesis were required for HSC formation (17). Molecular profiling approaches were used to determine the optimal ex vivo modulation conditions (e.g., temperature, time, concentration, and media) to enhance HSCs in a clinical setting. A phase I trial was performed to evaluate the safety and therapeutic potential of ex vivo modulation of a single UCB unit using dmPGE2 (ProHema) prior to reduced intensity double UCB transplantation (5).

Cord Blood Transplantation Without Host Preconditioning: Will There Be GVHD?

The possibility of using cord blood in the absence of host preconditioning would open up the door for a multitude of stem cell therapeutic applications. The current dogma among cord blood transplantations is that administration of allogeneic cord blood, even if HLA matched, would, in the best case scenario, lead to immunologically medicated suppression or rejection of the graft and, in the worst case, cause GVHD. Here we provide rationale for the preliminary clinical exploration of cord blood administration in a nonpreconditioned host.

If cord blood can be administered into a nonpreconditioned patient without fear of GVHD, then the next question

arises as to whether the infused cells will actually endow some type of benefit or be rapidly cleared by the immune system. Furthermore, even if transplanted cells are cleared by the immune system, it is known that apoptotic cells can mediate various therapeutic anti-inflammatory effects that are clinically relevant (19).

Mesenchymal Stem Cells Do Not Need Myeloablation for Efficacy

This also raises the possibility that due to the unique immunological properties of both the stem cell and non-stem cell components of cord blood, it may be possible to utilize allogeneic cells for regenerative applications without needing to fully compromise the recipient immune system (16). Currently, MSCs are being explored to regenerate damaged tissue and treat inflammation resulting from cardiovascular disease and myocardial infarction, brain and spinal cord injury, stroke, diabetes, cartilage and bone injury, Crohn's disease, and GVHD (4,15,26). Despite the fact that BM represents the main available source of MSCs, the use of BM-derived cells is not always acceptable due to the high degree of viral infection and the significant drop in cell number and proliferative/differentiation capacity with age (27). Recent studies also involve the transplant of MSCs from umbilical cord (14,20).

Overcoming Allogeneic Barriers to Cellular Therapies With Banked Cord Blood

UCB mononuclear cells have consistently been found to rescue neurons and oligodendrocytes from apoptotic cell death in both in vitro and in vivo models of stroke (28). These effects are most pronounced when UCB mononuclear cells are administered intravenously at delayed time points after the stroke, when apoptotic and inflammatory poststroke injury cascades predominate. The intravenous route of delivery ensures that the UCB cells are subject to full immune surveillance, making it essential to address issues of immune interactions between the donor UCB cells and the recipient's immune cells in the preclinical development of UCB cell therapy.

CONCLUSION

UCB has established itself as a legitimate source for hematopoietic stem cell transplantation. It is also considered an accessible and less immunogenic source for mesenchymal, unrestricted somatic, and for other stem cells with multipotent properties. The author also noted that researchers are expanding the use of cord blood to nonpreconditioned adult recipients for a regenerative purpose, which would be a major step for the practical advancement of stem cell therapeutics. By overcoming allogeneic barriers in regenerative medicine, the fundamental limitations of autologous cell therapy may result in effective standardized "off-the-shelf" cellular products for regenerative therapeutics. This major step can only be performed by understanding the unique immunology of cord blood grafts, leveraging the graft's regenerative capability for specific indications and identifying methods of amplifying cellular effects through administration of various drugs.

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