Stem Cells

Potential Therapy for Neonatal Injury?

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KEYWORDS

• Stem cells • Hematopoiesis • Cord blood • Transplantation • Neonate • Injury

KEY POINTS

- Umbilical cord blood (CB) contains a plethora of stem cells and multipotent progenitor cells (MPPs).
- In preclinical animal models, transplantation with CB or specific stemlike cells can limit brain and lung injury and/or preserve or restore function in part through antiinflammatory mechanisms.
- The few human studies to date suggest the short-term safety of CB-derived stem cells; however, additional preclinical and human studies are needed to establish therapeutic efficacy and long-term safety.

INTRODUCTION

Stem cell transplantation (SCT) is an established first-line or adjunctive therapy for a variety of neonatal diseases, including those involving inborn errors of metabolism, types of primary immune deficiencies, certain neutrophil disorders, and hematologic malignancies, such as neonatal leukemia. The utility of SCT in these and related conditions has been extensively discussed in the literature and is beyond the scope of the present review.[1–6] This article briefly summarizes current understanding of human stem cell biology during ontogeny and presents recent evidence of the potential role of SCT for the treatment of postinsult neonatal injury.

Disclosure Statement: The authors have no conflicts of interest relevant to the present review to disclose.

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Clin Perinatol 42 (2015) 597–612

http://dx.doi.org/10.1016/j.clp.2015.04.008 **perinatology.theclinics.com**

0095-5108/15/$ – see front matter

STEM CELL BIOLOGY: A BRIEF REVIEW

Stem Cell Theory: Pluripotent Stem Cells and Tissue-Specific Somatic Stem Cells

Two main types of stem cells have been described: pluripotent stem cells (PSCs) and somatic stem cells. The PSCs are multipotent stem cells that can differentiate into all cell types in the body and include embryonic stem cells (ESCs) and inducible PSCs (iPSCs). Tissue-specific somatic stem cells give rise to organ-specific cell types. ESCs are first established from the inner cell mass of the blastocysts in a fertilized egg.[7–9] In vitro studies have shown that cultured ESCs display self-renewal ability and have the capacity for multilineage differentiation. ESCs can differentiate into cell types that include all 3 germ layers, and in vivo studies have shown that ESCs can form teratomas when inoculated into immune-deficient mice. Murine studies have shown that when a fertilized egg is injected with ESCs and implanted into a pseudopregnant dam, ESC-derived cells contribute to all embryonic cell types, forming a chimeric animal. The multilineage differentiation ability of ESCs both in vivo and in vitro highlights their potential utility for stem cell therapies. This therapeutic potential is accompanied, however, by ethical problems because ESCs can be derived only from fertilized eggs.

More recently, ESC-like PSCs have been established from postnatal mouse testis and adult mouse/human somatic cells after the introduction of stemness genes, such as *Oct4*, *c-Myc*, *Sox2*, and *Klf4*.[10–12] These iPSCs overcome the ethical problems associated with ESCs; thus, iPSC biology and its possibilities for clinical applications have been the focus of intensive research. Although mouse ESCs/iPSCs have been shown to differentiate into somatic stem cells in vivo in chimeric animals, the induction of tissue-specific somatic stem cells from iPSCs remains a challenging problem. One primary reason for this is the difficulty in maintaining iPSC-derived stem cells in cell lineages that require rapid cell cycling of their progenitors to maintain cellular homeostasis (such as in the blood, skin, and skeletal muscles). Thus, the use of iPSCs to produce functional progenitor cells or even mature cells may be most successful when cellular targets have slow intrinsic cycling rates and thus do not require rapid somatic cellular replacement. Recent major advances in iPSC-derived cell therapy have been reported in a nonhuman primate spinal injury model and in a clinical trial of iPSC-derived retinal pigment epithelium replacement.[13,14]

According to currently accepted stem cell theory, each tissue in the body is maintained by tissue-specific stem cells with the capacity for self-renewal and specific lineage differentiation. During embryonic organogenesis, stem cells differentiate into lineage cells that form specific tissues. These stem cells are maintained in the tissues even during adulthood: for example, cell types, such as hair, skin, melanocytes, blood, muscle, intestinal epithelium, and sperm, are continuously regenerated by tissue-specific stem/progenitor cells. Although the healthy liver does not typically undergo tissue regeneration, if damaged the liver becomes a regenerative organ. Stem/progenitor cells, which have been identified in every tissue/organ, reside in a special microenvironment, called a niche, which facilitates the maintenance of self-renewal capacity. Although the brain and nervous system were not previously considered to have regenerative abilities, recent studies have identified stem/progenitor cells and their niches even in adult animals.[15–17] These cells may play a role in the maintenance of tissue homeostasis and can acquire the ability to produce lineage-specific cells for tissue regeneration after injury.

Recent technological advances have facilitated the identification, isolation, and purification of human somatic stem cells. The hematopoietic stem cell (HSC), the first stem cell to be experimentally proved in humans, resides in the bone marrow (BM)