

Preface

Perinatal brain injury is a leading cause of cerebral palsy (CP), often resulting in lifelong disabilities. Because more than 90% of CP patients today survive into adulthood, the economic and social burdens associated with support for the patients and their families are significant, and therefore pathophysiological understanding of the disease and development of effective therapies are urgent public health needs. Perinatal hypoxic–ischemic encephalopathy (HIE) is an important cause of brain injury resulting from reduced cerebral blood flow at birth that leads to hypoxia and hypoglycemia in brain cells. Impaired uptake of glutamate by brain neurons results in intracellular calcium accumulation, which ultimately causes irreversible damage. To date, hypothermia therapy has been the only effective treatment for HIE to prevent the development of CP. A recent publication in the United States [1], however, indicated benefits of autologous umbilical cord blood stem cell transplantation combined with hypothermia therapy for HIE, drawing attention to cell therapy for perinatal brain injury. This book, coauthored by leading physicians in the field, is intended to provide comprehensive and concise information to readers on the most recent advances in cell therapy for perinatal brain injury, from basic stem cell biology to clinical essentials.

Stem cells in umbilical cord blood were first discovered by Japanese researchers, Nakahata and Ogawa, in [2]. This led to a report by Gluckman et al. in [3] on the first clinical success of cord blood transplantation (CBT) in a patient with Fanconi's anemia. Since then, various public and private cord blood banks have been established and have provided cord blood units for transplantation to more than 30,000 pediatric and adult patients. CBT quickly gained importance also in Japan after the foundation of the Japanese Cord Blood Bank Network in 1999. Although initially limited to hematological disorders, CBT has found its application in inherited metabolic disorders since the turn of this century. In 2005, Escolar et al. reported a significant survival benefit of CBT in patients with early-stage infantile Krabbe disease [4]. According to their report, the 6-year mortality rate was 0% in 11 patients who underwent CBT from unrelated donors before the development of symptoms as opposed to an untreated cohort of 190 children who all died before reaching 8 years of age. In 2008, the potential of cord blood stem cells to differentiate into neural

cells was reported [5] and offered promising new uses of CBT and bone marrow transplantation in inherited metabolic diseases as reviewed by Prasad and Kurtzberg in [6]. Along with the reported clinical successes in inherited metabolic diseases, researchers in the field of brain injury began to devote their efforts to scientific studies on the role of CBT in central nervous system injuries associated with hypoxia and ischemia, exploring the potential of cord blood stem cells for brain regeneration.

In vitro experiments in [7] and [8] demonstrated the expression of neural and normal cell markers in human nucleated cord blood cells and the expression of oligodendroglial and astrocytic features in CD34⁺ and other cord blood stem cells. Through in vivo studies using a rat model of ischemic stroke, an improved outcome after intravenous administration of human cord blood stem cells to male rats was demonstrated in [9], and reduction in spastic paresis after intraperitoneal transplantation of human cord blood stem cells within 24 h of injury was reported in [10]. Although incorporation of the transplanted human mononuclear cells primarily around the lesioned brain area and engraftment 14 days posttransplantation were demonstrated, significant changes in lesion volume or differentiation into astrocytes were not observed. Thus, differentiation of human nucleated cord blood cells into neural cells observed in vitro was not confirmed in in vivo studies. These laboratory results are consistent with clinical data in humans. Kurtzberg et al. reported in [11] that donor-derived cells had differentiated into vessels, microglia, and choroid plexus cells but not into neuroectodermal cells (i.e., neurons, astrocytes, and oligodendrocytes) in the brain of a female infant with Krabbe disease who received CBT. These studies collectively suggest that transplanted cells do cross the blood–brain barrier and engraft in the brain but do not restore the lost function by differentiating into neural cells. Rather, it seems that these cells achieve clinical benefits through some other mechanisms that facilitate the repair of surrounding tissues.

The clinical efficacy of CBT in CP patients has recently been demonstrated. Autologous CBT in 20 CP patients in a study by Lee et al. in [12] and allogeneic CBT in 31 CP patients in a study by Min et al. in [13] both led to neurological improvements without serious adverse events. In the most recent study published in 2014, Cotten et al. [1] isolated stem cells from the autologous cord blood and administered them to cooled infants with moderate or severe HIE. The treatment was safe and resulted in significantly better intact survival with Bayley III scores of ≥ 85 compared with infants who received hypothermia therapy alone, although overall survival was not significantly different between the two groups. So, how does CBT work in the treatment of CP? Regulation of microglial response and facilitation of axonal sprouting have been indicated by recent studies. These findings suggest that the cord blood is capable of repairing brain damage through multiple endogenous pathways.

Although much of today's laboratory research focuses on embryonic stem cells and induced pluripotent stem cells that can differentiate into any type of tissue, these approaches have limitations in terms of clinical application to the treatment of perinatal HIE because they require a longer preparation and culture time, which may not fit within the short time window for optimal therapy. Allogeneic cells may

be stocked in advance, but this approach always comes with the risk of immune rejection. In contrast, cord blood, once considered medical waste, is an ideal source of stem cells for perinatal HIE as it obviates the ethical issues associated with the use of fetal cells and at the same time reduces the risk of rejection if autologous cord blood is used.

On August 6, 2014, the first clinical trial protocol for autologous cord blood stem cell therapy for neonatal HIE was approved in Japan. This trial is a new multicenter effort involving 11 CP research groups across Japan collaborating at all levels from the nonclinical to clinical phases to evaluate the safety and efficacy of autologous cord blood stem cell transplantation in HIE infants in combination with hypothermia therapy. Perinatal HIE is a leading cause of CP, and severe HIE occurs in one to six cases per 1000 live births. Despite effective treatment such as hypothermia therapy, severe sequelae still develop in 50% of patients. Because no effective treatment exists once brain damage has been established and CP symptoms have developed, neonatal management before the establishment of damage is crucial. In this context, CBT, in combination with hypothermia therapy, is a promising cell-based regenerative approach for preventing CP associated with perinatal brain injury.

References

1. Cotten CM. et al. Feasibility of autologous cord blood cells for infants with hypoxic-ischemic encephalopathy. *J Pediatr*. 2014;164(5):973–9.
2. Nakahata T, Ogawa M: Hemopoietic colony-forming cells in umbilical cord blood with extensive capability to generate mono- and multipotential hemopoietic progenitors. *J Clin Invest*. 1982; 70(6): 1324–8.
3. Gluckman E, et al. Hematopoietic Reconstitution in a Patient with Fanconi's Anemia by Means of Umbilical-Cord Blood from an HLA-Identical Sibling. *NEJM*. 1989; 321:1174–8.
4. Escolar et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. *NEJM* 2005;352(20):2069–81.
5. Domanska-Januck K et al. A novel, neural potential of non-hematopoietic human umbilical cord blood stem cells. *Int J Dev Biol* 2008;52:237–48 (review)
6. Prasad V, Kurtzberg J.B Cord blood and bone marrow transplantation in inherited metabolic diseases: scientific basis, current status and future directions. *Jnl Hematology* 2009;148:356–72.
7. Sanchez-Ramos JR et al. Expression of neural markers in human umbilical cord blood. *Exp Neurol*. 2001;171:109–15.
8. Buzańska L et al. Human cord blood-derived cells attain neuronal and glial features in vitro. *J Cell Sci*. 2002;115:2131–8.
9. Chen J et al. Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats. *Stroke* 2001;32:2682–8.
10. Meier C. et al. Spastic paresis after perinatal brain damage in rats is reduced by human cord blood mononuclear cells. *Pediatr Res* 2006;59:244–9.
11. Kurtzberg J, et al. Umbilical cord blood cells engraft and differentiate in neural tissues after human transplantation. *Biology of Blood and Marrow Transplantation* 2003;9:128–129.

12. Lee YH et al. Safety and feasibility of countering neurological impairment by intravenous administration of autologous cord blood in cerebral palsy. 2012 J Transl Med. 2012;23;10:58.
13. Min K et al. Umbilical cord blood therapy potentiated with erythropoietin for children with cerebral palsy: a double-blind, randomized, placebo-controlled trial. 2013 Stem Cells. 2013;31(3):581–91.

Osaka, Japan

Haruo Shintaku, M.D., Ph.D.



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