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Review

The Therapeutic Potential of Human Umbilical Cord Blood Transplantation for Neonatal Hypoxic-Ischemic Brain Injury and Ischemic Stroke

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Human umbilical cord blood (HUCB) cells are rich source of immature stem cells, which have the potential to repair lost tissue. Intractable central nervous system (CNS) disorders are important targets for regenerative medicine, and the application of HUCB cells is being investigated in animal models of CNS disorders. Transplantation of HUCB has induced functional improvements in these animal models due to multiple therapeutic effects including neuroprotection, anti-inflammation, angiogenesis, and neurogenesis. HUCB cells are easily available and safer than other stem cells used in transplantation therapy. In this review, we focus on HUCB transplantation as an encouraging therapeutic approach for animal models of neonatal hypoxic-ischemic brain injury and ischemic stroke.

Key words: umbilical cord blood, cell transplantation, neonatal hypoxic-ischemic brain injury, ischemic stroke, stem cells

Human umbilical cord blood (HUCB) serves as a source of nutrients and oxygen between a mother and fetus, and can be collected at birth using non-invasive procedures. HUCB is known as a rich source of stem cells, and is used in the treatment of various hematopoietic diseases [1, 2]. Recently, it was widely reported that the use of HUCB was not limited to the treatment of hematological disorders, and that HUCB can induce regeneration in the central nervous system (CNS) [3, 4]. HUCB cells have a history of clinical use in hematology and oncology, and unlike embryonic stem cells, can be collected easily and without controversy. Since perinatal and adult ischemic brain damage is a cause of mortality and severe neurologic disability, the promise of HUCB transplantation for the treatment of CNS disorders becomes even more compelling (Fig. 1).

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Stem Cell Populations of HUCB

HUCB is rich in hematopoietic stem cells (HSCs), a type of stem cell that is the source of most blood cell lineages [5]. In addition, a variety of non-hematopoietic stem cells have been identified. Mesenchymal stem cells (MSCs) [6, 7] are defined as being able to adhere to plastic and as expressing CD29, CD44, and CD105 but not the hematopoietic cell markers CD34

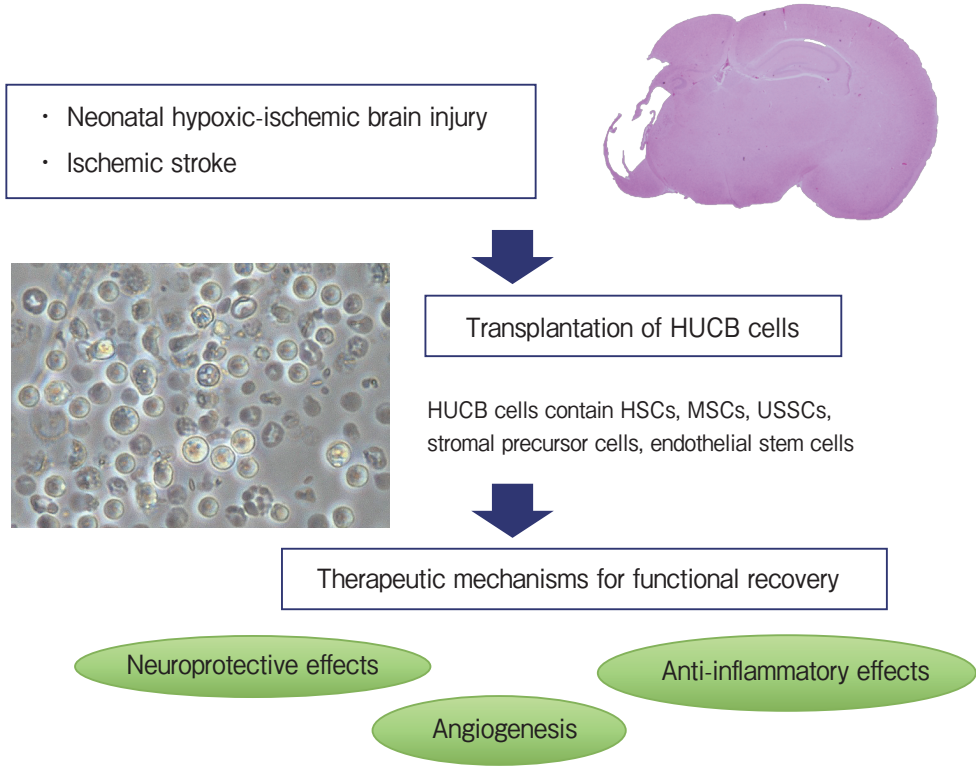

Fig. 1 The transplantation of human umbilical cord blood (HUCB) showed functional recovery in animal models of neonatal hypoxic-ischemic brain injury and ischemic stroke. The possible mechanisms of transplant therapy include neuroprotective effects, angiogenesis and anti-inflammatory effects. HUCB, human umbilical cord blood; HSCs, hematopoietic stem cells; MSCs, mesenchymal stem cells; USSCs, unrestricted somatic stem cells.

and CD45. Endothelial stem cells [8], stromal precursor cells [9], and still-not-fully-characterized populations of stem cells also exist in HUCB. Cells from the mononuclear fraction of HUCB are able to differentiate into multiple lineages under appropriate culture conditions [10]. Unrestricted somatic stem cells (USSCs) are also promising candidates as multipotent stem cells, which were isolated as a CD45-negative population from HUCB [11]. USSCs can be differentiated into osteoblasts, chondroblasts, adipocytes, and neural cells *in vitro*. Moreover, the *in vivo* differentiation of USSCs along mesodermal and endodermal pathways has been demonstrated in nude rat femurs. The *OCT4A* gene encodes one of the transcription factors that is important in maintaining the multipotency of HUCB stem cells as well as embryonic stem cells. Inhibition of *OCT4A* expression in HUCB stem cells inhibits cell proliferation and reduces multipotency [12]. Although these pluripotent stem cell populations are very rare, they may be helpful for the effective treatment of irreversible functional deficits.

HUCB Transplantation for Neonatal Hypoxic-Ischemic Brain Injury

Cerebral palsy is one of the severe neurodevelopmental sequelae of perinatal hypoxic-ischemic encephalopathy (HIE) [13]. There is currently no effective therapy for the functional regeneration of nerve tissue that is damaged during the perinatal period. The therapeutic potential of HUCB transplantation in animal models of HIE has been evaluated in several laboratories. The neonatal hypoxic-ischemic (HI) brain injury model has proved to be useful as an animal model of perinatal HIE [14, 15]. In this model, 7-day-old pups undergo unilateral common carotid artery ligation followed by systemic hypoxia, leading to unilateral brain damage in the hemisphere ipsilateral to the ligation. In rat models of neonatal HI,

intraperitoneal transplantation of HUCB-derived mononuclear cells led to the amelioration of spastic paresis. Human leukocyte antigen-positive transplanted cells were found not to express markers of neuronal cells, although the cells migrated from the intraperitoneal cavity into the damaged brain tissue and were detectable until 2 weeks after transplantation [16]. In another study, HUCB-transplanted rats showed functional improvement of their developmental sensorimotor reflexes; moreover, the number of cells expressing caspase-3 and activated microglia was significantly reduced in the striatum of HI rats [17]. Yasuhara *et al.* reported that mannitol, a blood-brain barrier permeabilizer, enhanced the expression of neurotrophic factors in neonatal HI-injured rats transplanted with HUCB [18]. Furthermore, HUCB transplantation normalized cortical processing and sensorimotor behavior assessed using *in vivo* electrophysiological recordings in the primary somatosensory cortex [19]. The latter study was the first to prove the link between cell transplantation and behavioral outcomes via the modulation of cortical reorganization and physiology following neonatal HI brain injury. However, other authors have found that HUCB did not improve motor function or attenuate brain damage after the intravenous administration of HUCB cells. A study using immunofluorescence and PCR analyses detected only a few HUCB cells in the brain [20]. For more effective treatment of neonatal HI brain injury, it is necessary to investigate optimal basic conditions such as cell dose, timing, and delivery route.

HUCB is currently being used for autologous transplantation in the treatment of cerebral palsy at a clinical trial conducted at Duke University, USA (NCT01147653) and the Medical College of Georgia, USA (NCT01072370). The preliminary results of this trial have been highly encouraging, and additional patients are being enrolled. Kochi Medical School (Japan) also started a clinical trial using autologous HUCB infusion for the treatment of children with cerebral palsy.

To date, the existing neonatal HI brain injury models do not accurately reproduce the pathological conditions of cerebral palsy. We are developing a novel mouse model of cerebral palsy to address these deficiencies by monitoring oxygen saturation levels. These model mice reproduce the motor deficits observed in cerebral palsy, and we are now investigating the therapeutic effects of HUCB transplantation in this model.

HUCB Transplantation for Ischemic Stroke

In the treatment of stroke, Chen *et al.* were the first to report the therapeutic effects of HUCB in a rat model of middle cerebral artery occlusion (MCAO) [21]. The intravenous administration of HUCB significantly ameliorated the behavioral deficits in this model, and grafted cells were detected in the injured brain at 7 days after stroke. Similar results were reported by Vendrame *et al.* [22], who demonstrated that HUCB transplantation significantly improved behavioral performance and reduced infarct volume after MCAO. Willing *et al.* investigated the delivery route of HUCB administration (intravenous versus intrastriatal) in a rat model of permanent MCAO. They found improvements in a number of behavioral tests after the transplantation of HUCB cells via both delivery routes. However, in the step test, significant improvements were observed only following the intravenous delivery of HUCB cells. This suggests that the intravenous delivery of cells is preferable to direct intraparenchymal delivery in the long term, and the observed functional recovery may be due to peripheral effects by systemic adminatration [23]. Furthermore, HUCB transplantation restored the MCAO-induced reduction of spleen size and depletion of the spleen $CD8^+$ population by increasing the production of interleukin-10 (IL-10), an anti-inflammatory factor. These results suggest the immunomodulatory mechanism by which HUCB mediates protection in the rat MCAO stroke model [24]. Treatment of HUCB with mannitol significantly increased the level of neurotrophic factors in the ischemic brain, which was correlated with reduced cerebral infarction volume and improvement of motor function [25]. Recently, Lim *et al.* reported that the intrathecal administration of HUCB-derived MSCs by lumbar puncture significantly reduced ischemic damage. Grafted cells were detected in the ischemic boundary zone and had differentiated into neurons and astrocytes by 28 days after transplantation [26]. These studies suggest that the administration of HUCB results in an amelioration of motor function and reduction of infarct volume and immunological responsiveness in animal models of

stroke.

Therapeutic Mechanisms

Neuroprotective effects. Reportedly, functional recovery following HUCB transplantation involves multiple mechanisms in HI injured animals. While many studies have proved the ability of HUCB cells to express neuronal, astrocyte, and oligodendrocyte markers *in vitro* [27, 28], only a small percentage of transplanted HUCB cells display a neuronal cell phenotype in the host brain. Functional improvement has been found at an early date after HUBC transplantation. It is quite unlikely that the grafted cells incorporated into the brain tissue and formed neuronal networks in the early days after transplantation. Thus, it is more likely that these cells act as a source of trophic factors in the CNS and peripheral organs. Glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), interleukin-1α (IL-1α), and stromal cell-derived factor 1α (SDF-1α) are consistently expressed by cultured HUCB cells [29, 30]. BDNF and NT-4/5 were also detected in the supernatants of HUCB cells. BDNF and NGF block caspase-3-mediated apoptosis and microglial activation in the ischemic brain; therefore, these neuroprotective factors may exert a beneficial influence on HUCB and the microenvironment in the injured neuronal tissue [31, 32]. Oligodendrocytes subjected to oxygen-glucose deprivation were rescued by co-incubation with HUCB cells via Akt Ser473 phosphorylation. The administration of HUCB increased Akt phosphorylation and reduced the cleavage of caspase-3 following MCAO. It was suggested that trophic factors from HUCB activated the PI3K/Akt signal transduction pathway to enhance the viability of cells exposed to ischemic conditions [33].

Angiogenesis. Angiogenesis is an important process playing a therapeutic role in ischemic injured tissue [34]. Taguchi *et al.* demonstrated that the transplantation of $CD34^+$ cells derived from CB induced angiogenesis at the ischemic boundary zone and resulted in endogenous neurogenesis in a mouse stroke model [35]. Suppression of endothelial proliferation by endostatin, an anti-angiogenic agent, diminished this endogenous neurogenesis. These data suggest that the neovascularization induced by the transplantation of $CD34^+$ cells is essential for survival and enhances neuronal regeneration after stroke. $CD34^+$ cells help to maintain the cerebral circulation during ischemic stress and secrete various angiogenic factors, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1) [36, 37]. HUCB-derived $CD34^+$ cells promote, directly or indirectly, an environment that is conducive to neovascularization of the ischemic brain. The transplantation of HUCB-derived MSCs was shown to promote the formation of new blood vessels and increased cortical blood flow in a rat model of MCAO [38]. Transplanted cells were observed around endothelial cells and shown to express VEGF and BDNF in brain ischemia models [39, 40]. In addition, the expression of Tie-2, an endothelial protein associated with angiogenesis, was increased after HUCB transplantation [40]. Angiogenesis is mainly regulated by the VEGF/VEGF receptor and the angiopoietin/Tie-2 signaling pathway [41]. According to these results, the formation of new blood vessels with increased cerebral blood flow in the ischemic brain might enhance neurogenesis and neuronal survival, thereby supporting functional recovery.

Anti-inflammatory effects. Ischemia in the brain elicits a strong inflammatory response; it triggers acute inflammation, which has been associated with an increase in brain damage [42].

In MCAO rats, a massive response by the peripheral immune system is activated at 6 hours after reperfusion [43]. After MCAO, activated spleen cells secrete significantly increased levels of inflammatory factors including tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-6 (IL-6), MCP-1, and interleukin-2 (IL-2). In HUCBC-treated MCAO rats, TNF-α and IFN-γ levels were significantly depressed compared to those in sham-treated rats. HUCB transplantation increased the levels of IL-10, rescued the stroke-induced reduction of spleen weight, and restored the depleted levels of spleen $CD8^+$ T-cells [24]. IL-10 is a regulatory cytokine that plays an important role in maintaining the anti-inflammatory environment within the CNS [44, 45]. The modulation of this immuno-inflammatory response is one of the protecting effects induced by HUCB trans-

plantation following ischemic brain injury. In the CNS, microglial cells are sensitive sensors of events occurring in their environment, and contribute to various inflammatory responses [46, 47]. Activated microglial cells facilitate oxidative injury, inflammatory responses, and neuronal cell apoptosis [48]. HUCB transplantation significantly reduces the number of activated microglia and blocks the infiltration of CD11b-positive amoeboid-shaped immune cells in the brain following HI injury [17]. HUCB may modulate the beneficial or harmful signals of microglia [49]. Newcomb *et al.* indicated that the therapeutic mechanism of HUCB transplantation preceded and ameliorated the massive infiltration of proinflammatory cells [50]. Thus, transplanted HUCB cells act through anti-inflammatory mechanisms that reduce the damage caused by the HI-induced immune responses.

Conclusions

HUCB transplantation is a promising treatment for perinatal and adult ischemic brain injury. The major advantages of HUCB cells are their availability, safety, immaturity, and heterogeneous properties. Distinct evidence from animal models clearly indicates that the transplantation of HUCB is a promising approach for the treatment of intractable CNS disorders in the future.

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