

News Release

Title

Intravenously delivered Multilineage-differentiating stress enduring cells dampen excessive glutamate metabolism and microglial activation in experimental perinatal hypoxic ischemic encephalopathy

Key Points

- Intravenously administered Muse cells dramatically ameliorated the behavioral abnormalities in the perinatal HIE model until adolescent (for 5 months) without any immunosuppressants.
- Muse cells were engrafted in the injured brain and differentiated into neural cells over 6 months after injury.
- Muse cells suppressed excitotoxic brain metabolites and attenuation of microglial activation after injury.
- The present study supported the feasibility of intravenously administered donor-derived allogeneic Muse cells for clinical trials in HIE without HLA matching or immunosuppressant treatment.

Summary

Dr. Toshihiko Suzuki (first author), Prof. Yoshiaki Sato (corresponding author), Prof. Masahiro Hayakawa in Division of Neonatology, Center for Maternal-Neonatal Care, Nagoya University Hospital, Prof. Yoshiyuki Takahashi in Department of Pediatrics, Nagoya University Graduate School of Medicine, Prof. Masaaki Mizuno and Prof. Shinobu Shimizu in Department of Advanced Medical Development, Nagoya University Hospital, collaborated with Prof. Mari Dezawa in Tohoku University Graduate School of Medicine, Prof. Cesar V Borlongan (corresponding author) in South Florida University, and Life Science Institute Inc.(LSII) have clarified the possibility of a new treatment using Multilineage-differentiating stress enduring cells (Muse cells) for perinatal hypoxic-ischemic encephalopathy (HIE), and its treatment mechanism.

Perinatal hypoxic-ischemic encephalopathy (HIE) is an ischemic brain injury caused by asphyxia in or around birth and is still the main cause of neurological disability and death. Currently, the only treatment for HIE is therapeutic hypothermia, but with limited effects particularly in severe cases. Therefore, the development of new therapies for perinatal HIE stands as an urgent clinical need.

Muse cells are a novel type of endogenous pluripotent stem cells, existing in peripheral blood, bone marrow, and organ connective tissues. Muse cells injected intravenously migrate into injured sites and spontaneously differentiate into functional cells even without artificial differentiation or induction.

In the present study, it was demonstrated that intravenously administered Muse cells in the perinatal HIE models were engrafted in the injured brains and differentiated into neural

cells without any immunosuppressants, and ameliorated brain dysfunction in behavioral evaluations. Muse cells also suppressed excitotoxic brain glutamate metabolites and attenuated microglial activation. These results indicate the feasibility of intravenously administered donor-derived allogeneic Muse cells for clinical trials in HIE.

Research Background

The remarkable progress in perinatal care has dramatically improved the survival rate of newborns, but the neurological outcome has not improved. Perinatal hypoxic-ischemic encephalopathy (HIE), an ischemic brain injury caused by asphyxia in or around birth, leads to cerebral palsy, mental retardation, and even neonatal death in some severe cases. Currently, therapeutic hypothermia is the only treatment option for HIE, but with limited effect, particularly in severe cases. Therefore, the development of new therapies is an urgent task in perinatal HIE.

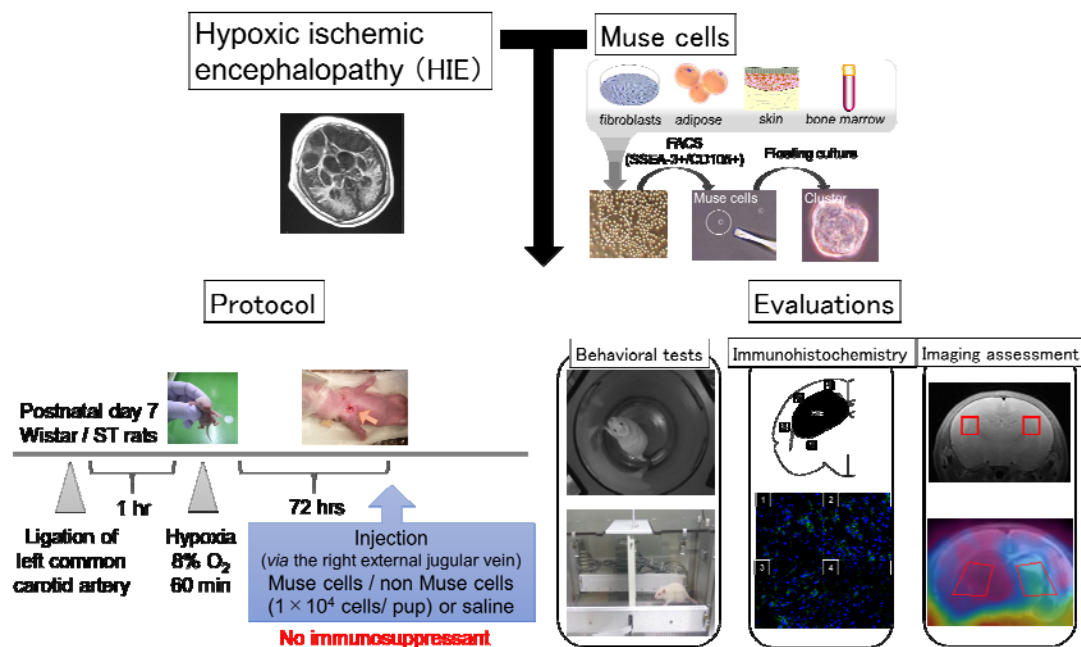
Recently, cell therapy using stem cells has been clinically applied to various diseases. Our research group focuses on the cells called “Multilineage-differentiating stress enduring cells (Muse cells)” as a new treatment for HIE. Muse cells are a part of the mesenchymal stem cells, and harvested from bone marrow (BM), blood and organ connective tissues. They display endogenous pluripotent-like property and express pluripotent surface marker, stage-specific embryonic antigen-3 (SSEA-3). Muse cells exhibit several unique transplantable cell features including non-tumorigenicity, stress tolerance, self-renewal. Moreover, since Muse cells possess an immunomodulatory system similar to the placenta, they have a low risk of immune rejection. Muse cells injected intravenously migrate into injured sites and mediate tissue repair via tissue-specific differentiation. Based on these attractive translational properties, clinical trials for stroke, acute myocardial infarction, epidermolysis bullosa and spinal cord injury have been initiated via Japanese regulatory authority, all based on intravenous drip of donor-derived allogeneic Muse cells without HLA matching or immunosuppressant treatment.

Therefore, we hypothesized that Muse cells could ameliorated impaired brain function by spontaneously migrating to injured brain tissue, differentiating into neural cells and repairing them, even for brain injury caused by hypoxia such as HIE. In the present study, we investigated the therapeutic effect of Muse cells for HIE model animals.

Research Results

Our research group administered Muse cells intravenously to HIE model animals without any immunosuppressants, and performed several evaluations such as brain images, behavioral tests, and brain tissue assessments. In the model animals at 1 month or 5 months after administration of Muse cells, significant functional improvements were observed in behavioral abnormalities (e.g. hyperactivity, open-field test), learning disabilities (active avoidance test, novel object recognition test), and movement disorder (i.e. paralysis, cylinder test). In the brain tissue assessment, it was demonstrated that Muse cells were engrafted only around the damaged brain tissue over a long period of 6 months after brain injury, even without

immunosuppressants. Moreover, Muse cells differentiated into neural and glial cells. Despite the long-term engraftment of Muse cells in the brain, no side effects were observed after administration of Muse cells, and there was no tumorigenesis or no increased mortality. In the brain imaging assessment 2 days after Muse cell administration, it was found that the suppression of excitotoxic brain glutamate metabolites and attenuation of microglial activation in the Muse group. In addition, in vitro experiment using the co-culture of microglial cells and Muse cells also demonstrated that Muse cells attenuated the microglial activation. In the early stage of cerebral ischemia with hypoxia, irreversible neural cell damage occurs by progressing anaerobic metabolism, and over-producing lactic and glutamic acid. Once it happened, microglia in the brain are activated to cause further neural inflammation and injury. Muse cells broke the vicious cycle of neural inflammation and damage possibly through the suppression of excitotoxic brain glutamate metabolites and attenuation of microglial activation.



Research Summary and Future Perspective

Intravenously administered muse cells remarkably improved the behavioral abnormalities in the perinatal HIE model possibly through engraftment of Muse cells in the injured brain and their differentiation into neural cells, suppression of excitotoxic brain metabolites and attenuation of microglial activation. The present study suggests that intravenous administration of Muse cells can be a novel treatment for HIE. As Muse cells have an immunomodulatory property to reduce the risk of immune rejection, donor-derived Muse cells can also be administered intravenously without immunosuppressants. Currently, clinical trials are underway in Japan to administer donor-derived Muse cell products by intravenous drip for some adult diseases such as myocardial infarction. Based on the findings of the present study, we are conducting an exploratory investigator-initiated clinical trial using clinical-grade Muse cells for HIE.

Publication

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