Environmental enrichment important factor impacting cell transplantation and brain repair

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A team of Korean researchers investigated whether "environmental enrichment" can improve the neurobehavioral function of six week-old mice after transplantation of adipose-derived stem cells (ASCs) to treat hypoxic-ischemic brain injury, and found that brain repair (neurogenesis) was aided in some animals through exercise-induced fibroblast growth factor 2 (FGF2), a strong pro-angiogenic factor.

The post-transplantation environmental enrichment (EE) included use of a running wheel and exposure to "novel objects."

The study appears as an early e-publication for the journal *Cell Transplantation*, and is now freely available online.

"FGF2 was synergistically enhanced in the striata of mice treated with EE after ASC transplantation," said study co-author Dr. Sung-Rae Cho of the Yonsei University College of Medicine in Seoul, Korea. "The underlying mechanisms of this synergism included an enhanced repair process, such as higher engraftment of the transplanted ASCs, increased endogenous neurogenesis, and astrocytic activation coupled with the increase in FGF2."

Astrocytes, star-shaped brain cells that are also the most abundant brain cell, perform many functions, including supporting the cells that form the blood–brain barrier and providing nutrients for nervous system

tissue. Multipotent ASCs have been used for promoting angiogenesis (blood vessel growth) and are also known to secrete potentially beneficial growth factors.

"Hypoxic-ischemic brain injury is a major cause of damage to the fetal and neonatal brain," said Dr. Cho. "The majority of affected children demonstrate neurodevelopment impairment. However, cell-based therapy has emerged as a potential treatment. In this study we applied EE in the chronic stage of impairment and studied its synergistic effects in the test mice at six weeks, five weeks after induced brain injury."

The authors noted that cerebral palsy has been associated with hypoxic brain injury, resulting in "considerable incidence or morbidity." They also noted that exercise has shown to be beneficial to children with CP. However, they also reported that ASC transplantation in animal models of CP has yet to be studied.

The researchers concluded that, compatible with other studies, EE increases endogenous cell migration to an ischemic injury and facilitates functional repair.

"The role of FGF2 as a mediator of the effects of exercise on the brain, and that FGF2 can be induced by physical exercise and regulated in an activity-dependent fashion, raises the possibility that FGF2 is involved in behavioral function," explained Dr. Cho. "We propose that the increase in FGF2 may provide a favorable microenvironment for repair purposes, and thus contribute to functional recovery."

They concluded that a rehabilitative strategy of cell-based therapy coupled with environmental enrichment could be effective for treating CP and other neurological diseases, including adult stroke.

"This study highlights the potential impact that combination therapies,

such as stem cell transplantation and rehabilitation, could have on brain disorders, possibly due to their interaction with survival or integration of the implanted cells or to modulation of the host microenvironment," said Prof Stephen Dunnett of Cardiff University's Brain Repair Group, "but it is important to emphasise that such initial observations are a very long way from yet providing a clinical therapy. We still need to understand the mechanisms by which implanted cells and growth factors work together to enhance functional recovery, we need better animal models to test the cells that are directly relevant to the specific human disorder targeted, and there are profound technical and safety issues still to be resolved before such novel stem cell strategies can be used safely in first-in-man clinical trials".

More information: Seo, J. H.; Kim, H.; Park, E. S.; Lee, J. E.; Kim, D. W.; Kim, H. O.; Im, S. H.; Yu, J. H.; Kim, J. Y.; Lee, M-Y.; Kim, C. H.; Cho, S. R. Environmental enrichment synergistically improves functional recovery by transplanted adipose stem cells in chronic hypoxic-ischemic brain injury. Cell Transplant. Appeared or available online: February 4, 2013. http://www.ingentaconnect.com/content/cog/ct/pre-prints/ct0633seo.

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