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Akt Pathway 'ramp ups' effects of transplanted umbilical cord cells used in stroke therapy

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Researchers have known that transplanted human umbilical cord cells (HUCBCs) can have a restorative effect on the brain and brain function following a stroke. However, just how the cells exert their therapeutic effects has not been clear. Now, a research team from the University of South Florida using animal models of stroke has found that the HUCBCs are most beneficial in preventing neuron loss when the Akt signaling pathway is activated by secretions from the HUCBCs and that Akt activation subsequently impacts a specific gene involved in reducing inflammation. A reduction in inflammation can help neural cell survival following a stroke.

The study will be published in a future issue of *Cell Transplantation* and is currently freely available on-line as an unedited early e-pub.

"Stroke is the fourth leading cause of death and the leading cause of disability in the U.S.," said study lead author Dr. Alison E. Willing. "The goal of our study was to identify HUCB-induced neuronal genes associated with cell survival following a stroke and to discover just how soluble factors secreted by HUCBCs induce critical signaling pathways in neurons that enhance cell survival."

Four groups of laboratory rats modeled with stimulated stroke by oxygen or glucose deprivation were treated with or without HUCBCs. When the activation of the Akt pathway was confirmed in the HUCB-treated

group, researchers found that the treated group had a 44 to 68 percent reduction in neuron loss when compared to the untreated groups.

"Our observations show that HUCB neuroprotection is dependent on the activation of the Akt signaling pathway that increases the transcription of the Peroxiredoxin-5 (Prdx5) gene," explained Dr. Willing. "This finding suggests that HUCBC therapy could be a promising treatment for stroke and other forms of brain injury when gene expression is modified to promote neural protection."

While pathways other than Akt have been shown to be important in cell survival, Akt has been shown to be more important than others because it works to activate Prdx5, an antioxidant enzyme gene with the primary function of reducing hydrogen peroxide and inflammation. Prdx5 plays a significant role in the regulation of the transportation of certain molecules in apoptosis, or 'programmed cell death." Antioxidants have been shown to limit cell death and levels of Prdx5 have been found to be lower - and inflammation higher - in patients with more severe strokes.

"This finding implies that in severe stroke Prdx5 is either degraded or its production is impaired," says Dr. Willing. "Prdx5 may be an important component of the antioxidant effect of HUCBCs and, therefore, a candidate for therapeutic targeting of oxidative stress in stroke."

The researchers concluded that HUCBCs "rescued" neural cells and prevented neuronal loss in rats modeled with stroke by increasing the transcription of genes related to survival and repair by inhibiting inflammation. It was the "ramping up" of Prdx5 through the Akt pathway that facilitated this effect.

"The neurosurvival action of secretants through Akt signaling not only ramped up transcription of Prdx5 and other survival-associated genes, but also inhibited genes that play a detrimental role in stroke injury,"

they concluded.

"This study provides hope of a treatment for stroke using HUCBCs, which are easily obtained, avoid ethical issues and have a minimal chance of rejection compared with other allogeneic stem cells, in order to rescue endogenous cells and restore function," said Dr. Shinn-Zong Lin, professor of Neurosurgery and superintendent at the China Medical University Hospital, TaiChung, Taiwan and Coeditor-in-chief of *Cell Transplantation*. "The study highlights the need for further understanding of the role of oxidative stress in the pathogenesis of stroke ."

More information: Shahaduzzaman, M.; Mehta, V.; Golden, J. E.; Rowe, D. D.; Green, S.; Tadinada, R.; Foran, E.; Sanberg, P. R.; Pennypacker, K. R.; Willing, A. E. Human Umbilical Cord Blood Cells Induce Neuroprotective Change in Gene Expression Profile in Neurons after Ischemia through Activation of Akt Pathway. *Cell Transplant.* Appeared or available on-line: November 13, 2014

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