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Optical Control of Neural Stem Cell Grafts in Experimental Stroke Model

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Introduction

It has been shown that the transplantation of stem cell progeny from multiple sources ameliorates motor deficits after stroke. However, it is currently unknown to what extent the electrical activity of grafted neural stem cell progeny participates in the improvement of motor deficits and whether excitatory phenotypes of the grafted cells are beneficial or deleterious to motor performances.

Methods

We first derived multipotent neural stem cells (NSCs) from human embryonic stem cells. The NSCs were then transduced with lentiviral vectors carrying the channelrodopsin-2 (ChR2) gene fused with enhanced yellow fluorescent protein (ChR2–EYFP) under the EF1alpha promoter. ChR2 is a transmembrane conductance regulator that when expressed by a cell, can generate action potentials in response to blue light stimulation. The ChR2 expression was confirmed in vitro. To test the function of these cells in stroke model, Sprague Dawley rats were subjected to 65 min middle cerebral artery occlusion. One week later, immunosuppressed rats were transplanted with NSCs (2 x 105) into the ischemic boundary zone in the striatum. Animals were biweekly tested for the use of their forelimbs in the cylinder test and for locomotor activity.

Results

After 12 weeks survival time, the animals were perfused and brains processed for histo-pathology and immunocytochemistry. Grafted NSCs, identified with a human-specific nuclear marker survived in the stroke-damaged peri-infarct tissue, expressed the ChR2 transgene and extended neurites into the host parenchyma. Our behavioral analysis demonstrated that light stimulation of animals grafted with the ChR2 optogenetically engineered NSCs increased their forelimb use in comparison to vehicle animals. In addition, animals that received the ChR2 expressing NSCs increased their motor activity and total distance covered during light stimulation relative to vehicle-treated animals subjected to light stimulation.

Conclusions

Our data suggested that excitatory influences of grafted neural stem cells may offer benefit in experimental stroke.

Learning Objectives

Optical stimulation of grafted neural stem cells affect motor recovery after stroke

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