Human neural stem cell grafts modify microglial response and enhance axonal sprouting in neonatal hypoxic-ischemic brain injury.

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Public Summary:
BACKGROUND AND PURPOSE: Hypoxic-ischemic (HI) brain injury in newborn infants represents a major cause of cerebral palsy, development delay, and epilepsy. Stem cell-based therapy has the potential to rescue and replace the ischemic tissue caused by HI and to restore function. However, the mechanisms by which stem cell transplants induce functional recovery are yet to be elucidated. In the present study, we sought to investigate the efficacy of human neural stem cells derived from human embryonic stem cells in a rat model of neonatal HI and the mechanisms enhancing brain repair. METHODS: The human neural stem cells were genetically engineered for in vivo molecular imaging and for postmortem histological tracking. Twenty-four hours after the induction of HI, animals were grafted with human neural stem cells into the forebrain. Motor behavioral tests were performed the fourth week after transplantation. We used immunocytochemistry and neuroanatomical tracing to analyze neural differentiation, axonal sprouting, and microglia response. Treatment-induced changes in gene expression were investigated by microarray and quantitative polymerase chain reaction. RESULTS: Bioluminescence imaging permitted real time longitudinal tracking of grafted human neural stem cells. HI transplanted animals significantly improved in their use of the contralateral impeded forelimb and in the Rotorod test. The grafts showed good survival, dispersion, and differentiation. We observed an increase of uniformly distributed microglia cells in the grafted side. Anterograde neuroanatomical tracing demonstrated significant contralesional sprouting. Microarray analysis revealed upregulation of genes involved in neurogenesis, gliogenesis, and neurotrophic support. CONCLUSIONS: These results suggest that human neural stem cell transplants enhance endogenous brain repair through multiple modalities in response to HI.

Scientific Abstract:
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