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NEURODEGENERATIVE DISEASE

Giving survival a boost

Although it is the selective death of motor neurons that ultimately causes the symptoms of amyotrophic lateral sclerosis (ALS), the disease also renders other spinal cord cells, including astrocytes, dysfunctional. Maragakis and colleagues have now shown that the replacement of damaged astrocytes through precursor cell transplantation might be a useful therapeutic strategy for ALS.

The authors transplanted glial restricted precursors (GRPs) into the grey matter of the spinal cord in a transgenic rat model of ALS. With an eye on future clinical trial approaches, transplantation was carried out at spinal levels that would be likely to influence the respiratory motor neurons innervating the diaphragm, the loss of which is the primary cause of death in ALS.

Eighty days after transplantation, many of the cells had survived and differentiated into glial fibrillary acidic protein (GFAP)-expressing astrocytes. The absence of ubiquitylated inclusions and the continuing expression of the glutamate transporter GLT1 in these cells suggested that they had not succumbed to the disease process that affected host astrocytes within this period.

Importantly, the transplants had beneficial functional effects. Animals that received the transplants had extended survival times, and the progressive decline in their forelimb strength and motor performance was delayed, consistent with a focal effect of the transplant on cervical motor neurons. Furthermore, the decline in phrenic-nerve compound muscle action potentials, an indicator of lessening diaphragm function, was slowed. These improvements correlated with a reduction in cervical motor neuron death.

How did the transplanted cells mediate their beneficial effects? The authors found that GLT1 protein levels were higher in the spinal cord of the transplanted rats. Transplanting GRPs that lacked GLT1 did not alter disease progression, suggesting that the boost in GLT1 levels provided by the transplanted cells contributes to their effects. The microglial response to the disease was also attenuated in GRP-transplanted animals, indicating that reduced inflammation may also contribute to the effects of the transplant.

This study suggests that transplantation of precursors to replace damaged astrocytes might be a viable strategy to slow the progression of disease in patients with ALS, and highlights the importance of a healthy astrocytic environment for motor neuron survival.

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ORIGINAL RESEARCH PAPER Lepore, A. C. *et al.* Focal transplantation-based astrocyte replacement is neuroprotective in a model of motor neuron disease. *Nature Neurosci.* 19 Oct 2008 (doi:10.1038/nn.2210)