NEURODEGENERATIVE DISEASE

Taking stock of grafts

It was hoped that transplanting fetal dopaminergic neurons into the brains of patients with Parkinson's disease (PD) would provide a breakthrough in the management of the disease and possibly even lead to a cure. However, early evaluations of the results of these trials were mixed. Three independent groups of researchers have now assessed the long-term outcomes of these operations in patients who received transplants up to 16 years previously.

Many of the symptoms of PD are associated with the loss of dopaminergic neurotransmission in the striatum, which results from the progressive degeneration of the neurons that project to this region from the substantia nigra. The three groups investigated the brains of a total of six individuals (post-mortem) who had undergone transplantation of fetal midbrain tissue into the striatum between 9 and 16 years before their death. All three studies reported that the transplanted dopaminergic neurons had survived and integrated into the host tissue.

A key question is whether the relative youth of the implanted cells ensures that they remain healthy, or whether these cells too eventually succumb to the disease processes. Kordower and colleagues and Brundin and colleagues found evidence of α-synuclein-containing inclusions, Lewy bodies and Lewy-body-like pathology — all hallmarks of dopaminergic degeneration — in a small percentage of the grafted cells, suggesting that the disease indeed also occurs in these neurons.

By contrast, Isacson and colleagues observed pathology in the patients' brains, but no signs of α-synuclein aggregation or Lewy bodies in the grafted cells. The reasons for these differences remain unclear but might relate to differences in the transplantation protocols that were used, the tissue environments into which the cells were transplanted or the age of the cells at the time of death.

Isacson and colleagues also showed that the implanted midbrain cell population included some serotonergic neurons. As serotonergic neurons have been linked to the onset of dyskinesia in Parkinson's patients following treatment with L-Dopa, this suggests that it might be advantageous to remove these cells from the cell population before grafting.

These findings provoke mixed reactions. They indicate that grafted midbrain cells can survive for a significant period of time and, in some cases, produce clinical improvements. However, they also suggest that cells in the grafts are exposed to signals in the host environment or in the graft itself that mediate disease progression. A fuller understanding of the mechanisms that underlie this disease progression is therefore crucial if we are to understand both normal disease progression and how to produce more effective transplantation strategies.

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ORIGINAL RESEARCH PAPERS Kordower, J. H. *et al.* Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nature Med.* 6 Apr 2008 (doi:10.1038/nm1747) | Mendez, I. *et al.* Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years. *Nature Med.* 6 Apr 2008 (doi:10.1038/nm1752) | Li, J.-Y. *et al.* Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nature Med.* 6 Apr 2008 (doi:10.1038/nm1746)