

No evidence for disease-like processes in fetal transplants

On the back of recent reports showing Lewy body-like inclusions in a small percentage of transplanted dopamine neurons in Parkinson's disease (PD) over a decade after transplantation, Cicchetti et al. (1) now speculate that fetal grafts in Huntington's disease (HD) show a predisposition to disease-like processes 10 years after transplantation. Several points should, however, be taken into consideration when interpreting the data presented in this study, which we believe challenge the conclusions made by the authors.

To set the argument for graft degeneration between 18 months and 10 years after transplantation, the authors compare graft P zone and host striatal cell densities. However, this comparison is misleading because variable extents of host striatal degeneration in each patient and differences in fetal cell preparations could account for these modest changes. One can also question the clinical relevance of measuring the density of transplanted striatal neurons, given that <5% of the striatum is replaced by transplantation in each of the cases reported in Cicchetti et al. (1). In addition, supplemental data suggesting a necrotic graft in Patient 3 could alternatively show residual lipofuscin-containing inflammatory cells left from early needle-tract trauma after the original fetal tissue infusion and therefore not be representative of ongoing graft degeneration.

Even if degeneration does occur in the striatal transplants in HD a decade after transplantation, a more reasonable argument for the preferential loss of grafted striatal projection neurons is based simply on the differential vulnerability of striatal neurons to cellular stressors, as has been documented after ischemia (2). In such conditions of excitotoxicity and oxidative stress, striatal interneurons are relatively spared compared to projection neurons, a pattern similar to that observed in striatal neurons in HD. In addition, a recent study

of transplantation in an experimental model of multiple systems atrophy reports that transplanted striatal neurons have a reduced P zone volume when transplanted into the striatum of α -synuclein-overexpressing mice, compared to transplantation into WT mice (3). These points, together with a lack of primary HD pathology (nuclear inclusions and abnormal huntingtin immunoreactivity) in the grafted neurons, argue against disease-like processes affecting striatal grafts in HD.

The surgical complications observed in Cicchetti et al. (1), as suggested by the authors, may be associated with disease severity at the time of transplantation. However, this should not be pitched as a deterrent for future transplantation given that several other trials have not been associated with such complications (4). Striatal transplantation in HD can provide long-term clinical benefits (5). The inference made in Cicchetti et al. (1) that "grafts undergo disease-like neuronal degeneration" together with the negative position taken on the validity of fetal transplantation using these techniques seems speculative and misleading, is potentially damaging to ongoing HD (and PD) clinical transplantation studies and could slow down any future innovations of cell therapy.

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The authors declare no conflict of interest.

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