Lewy body pathology in long-term fetal nigral transplants: is Parkinson's disease transmitted from one neural system to another?

Until recently, it was believed that nigral neurons transplanted into brains of patients with Parkinson's disease (PD) are resistant to the disease process. This concept was based primarily on morphological evaluations of post-mortem brains from patients who had died within a few years after transplantation surgery (Kordower *et al*, 1995, 1997). These studies were performed before the creation of modern anatomical tools such as α-synuclein and ubiquitin immunohistochemistry that can better identify classic PD pathology. Our groups independently analyzed three post-mortem cases from patients grafted in the striatum with fetal nigral tissue between 11 and 16 years earlier (Kordower *et al*, 2008; Li *et al*, 2008). The surviving grafted neurons were numerous and provided dense dopaminergic innervation in the host putamen in all cases. Nonetheless, we found that some grafted neurons displayed pathological changes indistinguishable from those seen in the diseased host nigra (Kordower *et al*, 2008; Li *et al*, 2008). Indeed, we observed Lewy bodies (LBs), the hallmark pathology of PD. We found that the melanin- and tyrosine hydroxylase-containing neurons in the grafts contained α-synuclein and ubiquitin immunoreactivity. We confirmed that they were LBs by classic neuropathological stains such as hemotoxylin–eosin and thioflavin S, the latter being the definitive light microscopic marker of LBs. Several of the intracytoplasmic aggregates in the grafted neurons displayed a dense core surrounded by a lighter halo. This is the classic morphology of LBs found in catecholaminergic neurons in the substantia nigra and locus coeruleus, two regions that degenerate in PD, but distinct from the homogeneously stained LBs seen in the cerebral cortex in cortical LB disease. The proportions of pigmented neurons exhibiting LB markers in the grafts were similar to those seen in the host substantia nigra. In one of the long-term transplant cases we examined, the grafted cells also displayed another PD-related pathology, diminished dopamine transporter. This alteration suggests a compensatory response aimed at increasing the levels of dopamine in the synapses possibly due to the graft being under duress from PD.

Our findings impact the understanding of PD pathogenesis. They support the concept that the pathogenic process is chronically active in the PD brain and can attack transplanted nigral cells despite them being placed in an ectopic location (putamen). Interestingly, in our paradigm the grafted cells were aged only 10–15 years postnatally, which is far younger than the typical age at which PD affects nigral neurons. Braak *et al* (2003) have suggested that α-synuclein pathology gradually spreads throughout the neuraxis as PD progresses, and our observations could be the result of a similar phenomenon. We have speculated that a prion-like mechanism might explain how PD pathology can transfer from the host to the graft and that misfolded α-synuclein in host cells might promote misfolding and aggregation of the protein in adjacent grafted neurons (Braak *et al*, 2003; Brundin *et al*, 2008). The molecular mechanisms underlying disease propagation from the diseased host to a healthy graft are at present not clear, but remain a fascinating area for investigation that could be relevant for our understanding of how PD normally develops. Converging data support the roles of oxidative stress, excitotoxicity and neuroinflammation in PD pathogenesis and each can promote upregulation and misfolding of α-synuclein. It is intriguing to speculate that these pathogenic mechanisms, either alone or in combination, could also cause the development of LBs in the grafted neurons (Brundin *et al*, 2008).

While our results are a cause for concern for cell therapy in PD, the pathological events documented in these cases took over a decade to develop and therefore should not dramatically alter ones enthusiasm for dopamine cell replacement strategies. In open label assessments, patients in both series responded well for several years. In addition, many of the remaining dopaminergic neurons in the grafts appeared healthy and densely innervated the Parkinsonian striatum. To the extent that the grafted patients' clinical condition declined beyond a decade after grafting, it may have been due, at least in part, to the emergence of non-levodopa responsive symptoms. This limitation of the dopamine cell replacement strategy has always existed and is not altered by the findings of LBs in grafted neurons. Thus, whatever level of enthusiasm one had for the dopamine cell replacement strategy before these neuropathological findings should be sustained when considering the benefits of cell transplantation in PD in the future.

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DISCLOSURE/CONFLICT OF INTEREST

Both authors declare they have no conflict of interest related to the material presented in this paper.

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