NEURODEGENERATIVE DISEASE

Development of a new preclinical model of Parkinson's disease

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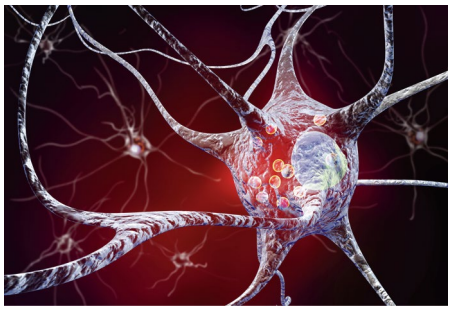
Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by the loss of dopamine-producing neurons in the substantia nigra and subsequent reduction of dopamine levels in the striatum, which results in motor impairment. Stem cell transplantation strategies aimed at replacing lost dopamine neurons have shown promising results in preclinical studies, but most of these studies have used toxin-induced models of PD, such as the 6-hydroxydopamine (6-OHDA) rodent model, which do not fully recapitulate human disease and might not predict the long-term effects of the host environment on the transplanted cells.

A study in *PNAS* describes the development of a new rat model with accelerated and progressive PD-like pathology, which was used to assess the long-term outcome of stem cell transplantation. The model was obtained by coinjection of human adeno-associated virus (AAV)-α-synuclein and human preformed α-syn fibrils (PFF) in the substantia nigra of female Sprague-Dawley rats (SynFib-injected rats). Approximately 50% of the SynFib rats showed motor impairment 4 weeks after AAV-α-syn/PFF injection, which was sustained at 16 weeks. Further analysis revealed that SynFib rats showed extensive pSyn pathology in the substantia nigra at 4 weeks and dopamine neuron cell death at 16 weeks. Microglial activation in the substantia nigra and striatum was greater at 4 weeks than at 16 weeks, which indicates that microglia are activated and recruited early to the areas of pSyn pathology. Altogether, these findings provide a time window to apply and assess different therapeutic neuroprotective interventions in this model.

To assess the effect of PD pathology on transplanted cells, human embryonic stem cell (hESC)-derived dopamine neuron progenitors were injected into the striatum of the rats 8 weeks after the combined injection into the nigra. "The key components of the model—overexpressed α-syn, PFFs, and grafted neurons—are all human, analogous to the patient brain environment, and therefore provide a 'humanized' system for studies," explain the investigators in their report. A group of 6-OHDA rats transplanted with hESC-derived dopamine neuron was used as a control.



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Analysis of the grafts 6 weeks after transplantation using an antibody recognizing human-specific neural cell-adhesion molecule (hNCAM) revealed that the inflammatory and pathological environment of the striatum in the SynFib model did not affect the survival of the transplanted cells and their ability to undergo maturation, compared with the 6-OHDA group. The host environment in the SynFib group also did not influence the ability of the transplanted cells to integrate into host striatal circuit.

At 12–18 weeks post-transplantation, both SynFib and 6-OHDA groups showed infiltration of host derived microglia into the core of the grafts, which were activated and present in higher numbers in the SynFib model than in 6-OHDA rats. In SynFib-grafted rats, the microglia contained small deposits of pSyn, a phenomenon that was absent in the 6-OHDA animal. pSyn deposits were also observed in dopamine neurons in the graft core of SynFib rats but not in the 6-OHDA rats. Confocal microscopy confirmed the presence of pSyn within the cytoplasm and in some cases also the nucleus of the neurons, suggesting host-to-graft transfer of pathology.

A similar phenomenon had been previously observed in patients with PD treated with fetal ventral midbrain transplants to replace dopamine neurons. Although early clinical trials had shown that fetal ventral midbrain transplantation can provide long-term clinical benefits, a small percentage of grafted neurons developed Lewy bodies, which suggested host-to-graft disease propagation. The transfer of α-syn pathology has not been reported in neurons grafted in toxin models and had therefore not been studied yet.

"While as yet we do not know the long-term consequences of the presence of pathology in grafted neurons, the humanized and accelerated xenograft model developed here in provides unique possibilities to do so," say the investigators in the discussion. In addition, the model would be valuable to evaluate whether patient's induced pluripotent stem cells (iPSC)-derived dopamine neurons are more vulnerable to host-to-graft transfer of pathology than neurons derived from healthy donors.

Alexandra Le Bras

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