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Non-autonomous cell death in Parkinson's disease

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Parkinson's disease (PD) is a relentlessly progressive neurodegenerative disorder, characterised by symptoms of bradykinesia, rest tremor, and rigidity, due to the loss of dopamine (DA) neurons. Intracellular accumulation and aggregation of α-synuclein in Lewy bodies and neurites accompanies the loss of DA neurons. Why DA neurons degenerate and α-synuclein aggregates in patients with PD is poorly understood. Three recent articles in *Nature Medicine* provide important clues to the underlying degenerative process and suggest that the loss of DA neurons and the aggregation of α-synuclein is mediated, in part, by a non-cell-autonomous process.[1–3]

Three independent groups did post-mortem neuropathological examinations of patients who had fetal mesencephalic dopaminergic transplants 4–16 years earlier. All three teams observed long-term survival of the grafts and indices of DA neuron survival consistent with the beneficial effect of transplantation in these patients. Two of the teams observed α-synuclein-positive Lewy bodies in the grafted neurons of 11-year-old, 14-year-old, and 16-year-old transplants.[1,2] Additionally, the Lewy bodies in the grafts stained positive for ubiquitin and α-synuclein was phosphorylated at Ser129, which is a marker of pathogenic α-synuclein. Increased α-synuclein accumulation was also seen in the older grafts. Patients who died up to 4 years after transplantation had no Lewy body inclusions; therefore, α-synuclein accumulation appears to be an age-dependent process. In all three patients there was evidence of activated microglia, suggesting an immune reaction. One of the patients had extensive microglial infiltration despite an initial marked improvement in motor function, which might have contributed to graft failure and loss of motor improvement.[1] The third team reported no microglial infiltration in five patients who had previously had fetal midbrain cell suspension grafts. In contrast to the other two reports, none of the fetal grafts showed pathology.[3]

Despite their incongruence, when taken together the findings of these three studies suggest that an active immune response might contribute to the degenerative process of PD, including the aggregation and accumulation of pathogenic α-synuclein. Only the transplants that had indices of microglia activation had pathological abnormalities, which might be related to the transplant procedure: patients who received grafts of solid pieces of ventral midbrain had pathology, whereas patients who received fetal cell suspensions did not. Thus, future clinical transplantation of DA neurons will need to avoid scenarios that contribute to an immune reaction. Consistent with this notion is the observation that parkinsonian mice that received self-derived DA neurons after somatic cell nuclear transfer do better than mice that received non-self grafts.[4] Future clinical studies in humans might be able to avoid

immune reactions by transplanting DA neurons from self-derived, inducible, pluripotent stem cells.

What do these studies teach us about the pathogenesis of PD? Clearly, non-cell-autonomous processes contribute to the degeneration of DA neurons. These processes seem to be initiated by microglia, at least in the grafts. Evidence from the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxication model of PD in mice has already suggested that the loss of DA neurons occurs by a non-autonomous process through microglial-induced degeneration of DA neurons by nitric oxide and other microglial-derived toxins.[5] Moreover, post-mortem examinations of humans who received MPTP showed active microglia, which indicates that chronic inflammation suggestive of a non-cell-autonomous process contributes to the death of DA neurons.[6] Indices of chronic inflammation are also seen in patients with sporadic PD.[7] Thus, as has been previously suggested, the loss of DA neurons is due not only to intrinsic abnormalities but also to their microenvironment.[5] Activated microglia are most likely to be responsible because they produce reactive oxygen and nitric oxide species, which accelerate the aggregation and accumulation of α-synuclein. From what was seen in the transplants, activated microglia set forth feed-forward, self-propagating mechanisms that contribute to the pathology of PD. Thus, any future clinical studies of neuroprotection will need to consider interfering with these non-cell-autonomous factors if any headway is to be made in identifying drugs that halt the progression and degenerative processes of PD.

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