Editorial

Embryonic Stem Cells and Parkinson's Disease: Cell Transplantation to Cell Therapy

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Although levodopa is currently a well-endorsed form of treatment for Parkinson's Disease (PD),[1] the search for a safe, long-term and dyskinesia-free treatment remains an agenda for many clinicians and scientists alike. Amongst others, restorative cell therapies are considered a potential treatment for this debilitating disease. A pursued tissue source in past studies has been the foetal ventral mesencephalon (VM). Earlier studies revealed that transplantation of foetal VM into hemiparkinsonian rats could restore the damaged nigrastriatal pathway.[2] Evidence in ameliorating symptoms and survival, maturation and reinnervation of dopaminergic neurons was so convincing, that transplantation into humans followed shortly thereafter.[3] Several open label trials have since been conducted.[2] However, outcomes following transplantation of fetal VM in humans have been variable (with little, to no effects in improved motor behaviour scores in some patients) compared to outcomes from earlier studies of VM transplantation into rodents.[4] In the best cases, dopaminergic neurons have survived the transplantation procedure, released dopamine and alleviated some of the motor symptoms in patients. Unfortunately, some patients also suffered graft-induced dyskinesias, the underlying triggering mechanism remaining unclear to date.[5] It was the observations from 2 double-blinded placebo-controlled trials that have largely placed a halt to this research.[6,7] The results indicated that there was discordant positron emission tomography, histology and clinical correlation and graft-induced dyskinesias in many patients. However, much discussion has since been raised about the outcomes of these trials compared to the earlier open label trials. Details that may explain some of the outcomes may relate to the older age of patients, the storage conditions of the tissue prior to transplantation, the lack of immunosuppression in one trial or limited use (6 months) in the other trial. Nevertheless, the outcomes resulted in re-evaluation of the use of such tissue for further transplantation into humans.

Much attention has subsequently been re-directed to potential new sources for cell replacement therapy. One of these cell sources is human embryonic stem cells (hESCs). These hESCs may overcome 2 major barriers that fetal transplants faced: i.e. ethical concerns over source of tissue and lack of tissue for widespread adoption. Furthermore, considerable knowledge from earlier fetal transplantation trials may be beneficial for future transplantation of hESCs. Once isolated as a cell line in-vitro, these cells derived from the inner cell mass of developing blastocysts have the capability of undergoing infinite self-renewal. They also maintain a capacity to form any cell type of the body. These unique cell properties have triggered a huge expanse of research in streamlining the direction of this differentiating ability into specialised cell types, suitable for transplantation and treatment of a wide variety of diseases.

In the case of PD, it is envisaged that hESC-derived dopaminergic neurons may be transplanted directly into the striatum of the brain, whereby they can extend axonal fibres, form synapses with host neurons and directly secrete and release dopamine to restore the impaired nigra-striatal pathway. To date, transplantation studies of ESC-derived dopaminergic neurons have been conducted in non-human, parkinsonian models, including 6-hydroxydopamine (6-OHDA)-lesioned rodents and 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine-treated rodents and monkeys. In studies using the 6-OHDA unilaterally lesioned rodent, improvement in drug-induced rotational scores have been observed over time.[8-14] Although, it can be argued that transplanted mouse ESC-derived grafts perform better, in general, than hESC-derived grafts. Although the exact reasons for this are yet to be pinpointed, it could be due to xenografting issues such as immunoreactivity. Also, hESC-derived grafts need to be maintained for longer periods as neuronal differentiation and maturation rates are slower compared with mESC (reflective of gestational time differences). With the added intolerance of rodents to long-term immunosuppressive compounds such as cyclosporine, this can hinder the ability to maintain grafts in rodents for an extended time and thus, prevent behavioural improvements from being observed. Perhaps the 2 best transplantation studies published to date have been performed using mESC-derived cells. Both Kim et al and Rodriguez-Gomez et al reported a complete reversal in rotational scores in 6-OHDA unilateral lesioned rats

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receiving mESC-derived neurons. In the case of the latter paper, grafts could also elicit effects even up to 20 weeks following transplantation. These studies give great hope for the future development of hESC as a restorative cell therapy for PD.

Perhaps the single, most disturbing issue in the transplantation of hESC-derived cells relates to safety. Some transplantation studies have reported an incidence of tumours or teratomas following transplantion of pre-differentiated hESCs in the brain.[15,16] This presents as an unacceptable risk for patients and currently hampers the development of hESC-derived cell therapies. These tumours are thought to arise from residual undifferentiated ESCs or precursor cells that maintain their proliferative capacity in-vivo. A number of different strategies are currently being tested to overcome these risks. Some of these include the use of genetic modification to "knock-out" tumour-inducing activity in hESC,[17] purifying cells prior to transplantation using sorting technology[18] and inducing selective apoptosis of tumour-inducing cells.[19] The establishment of a pure, differentiated hESC population, that is safe and risk-free, is an important translational research goal for all areas of regenerative medicine. Overcoming this hurdle will push hESCs one step closer to the clinic.

There may be one company that is on the verge of performing the first clinical trial using hESCs. Geron has announced that it will soon be seeking FDA approval to inject hESC-derived oligodendrocytes to treat patients suffering spinal cord injury. It is also, in the longer term, investigating the possibility of transplanting hESC-derived neurons for treatment of PD. It is without doubt that hESC are fast approaching the clinic. What should be carefully tested, however, is the ability of these cells to survive and function and do so, without inducing any risk to the patient. What is not clear at this stage, is whether hESC-derived grafts in the brain may elicit graft-induced dyskinesias. Without a good rodent model to study this, this could be difficult to evaluate and perhaps better tested in non-human primates.

To conclude, hESC-derived cells can be produced in-vitro, transplanted in-vivo and improve motor-related deficits in 6-OHDA unilateral lesioned rodents. Studies are currently being tested to improve outcomes observed and reduce the risks associated with tumour overgrowth following transplantation. We are well on the road for churning hESC into a safe and effective treatment for PD, granted that we can prove their effectiveness and safety in non-human animals first.

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