Editorial

Stem Cell Replacement Therapies in Parkinson's Disease

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World Parkinson's Disease Day—which falls on 11 April—commemorates the birthday of the late physician and geologist, James Parkinson. All around the world, efforts are under way to increase public awareness of the condition first described by Parkinson over 200 years ago. Over the past 2 decades, Parkinson's disease (PD) is viewed as more a clinical syndrome than a single disease entity characterised by motor features of tremor, bradykinesia, rigidity and postural instability. The identification of several pathogenic genes and loci and the recognition of non-motor symptoms and prodromic features have redefined classification of PD and expanded the clinical spectrum of the disease.[1-6]

Despite advances made in the treatment of PD and various drugs that have since been added to the armamentarium, there is still no specific cure for the condition. Currently, available treatments focus primarily on relieving motor symptoms that result from degeneration of dopamine (DA) neurons in the substantia nigra. Thus, dopaminergic medicines are administrated to restore DA signalling. However, systemic administration of dopaminergic medicines are associated with adverse long-term side effects such as levodopa-induced dyskinesias. While deep brain stimulation is effective in select patients, it does not prevent progression of PD. Transplantation of DA-producing cells in brains of PD patients to replace degenerated DA cells has seen a resurgence in popularity due to successful generation of DA-producing cells via induced pleuripotent stem cells (iPSC) and advances in methodologies that enable the production of authentic midbrain DA neurons via embryonic stem cells (ESC).[7,8]

More than 3 decades ago, studies on transplantation of foetal ventral midbrain tissue in PD patients have shown that it provided long-term relief of motor symptoms in early-stage patients.[9] However, due to ethical concerns, limited availability and heterogeneity of tissues which may contain serotoninergic cells that led to troubling dyskinesias, this approach could not be adopted as routine clinical therapy.[10]

Recently, great strides have been made in cell transplantation in PD that leveraged on the significant advances made in stem cell research and in vitro midbrain dopaminergic (mDA) cell differentiation techniques.[11-13] Various sources of cells could now be used as starting materials to generate transplantable DA neurons or progenitors. Several human ESC lines are also available to provide unlimited renewable and bankable cells. Through these well established in vitro differentiation protocols, uniform authentic mDA cells can be generated, characterised, cryopreserved and distributed worldwide.[12,13]

One drawback of human ESC is immunogenicity of allografts. However, since the central nervous system is an immune-privileged site, the transplanted cells can survive for decades even after a short period of immunosuppressant has been applied. Another starting material that can be used to generate transplantable mDA cells is iPSC which is derived from somatic cells of patients.[7]

The advantage of using autografts is that it is less likely to suffer from immune rejection. However, there are some disadvantages. First, iPSC from patients may carry genetic risk factors that might make them less than ideal therapeutic materials. Second, the potential genomic instability and tumourigenic property of iPSC make extensive genetic testing—an extremely expensive approach—a necessity to guarantee the safety of transplanted cells. As such, use of induced neurons (iN) converted directly from somatic cells has been proposed. Like iPSC, however, iN has several intrinsic limitations that have led to a halt in its use. The limitations of iN include limited quantity that can be generated from somatic cells, safety concerns over the introduction of exogenous genes with viral vectors and highly variable quality of each batch of iN.[14,15]

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Prior to transplantation, several fundamental aspects must be addressed that include in vivo DA neuronal survival, identification of a transplantable stage during DA neuron differentiation and establishment of reliable and sensitive analytical methods capable of assessing the efficacy of transplantable DA neurons. In our previous work with PD rodent models, we showed that cells transplanted in the form of aggregates survived far better than single cells.[16] We also conducted systematic comparison analysis that identified optimal differentiation stages of DA cells most suitable for transplantation to achieve the best therapeutic effect. We investigated DA progenitors, immature DA neurons and DA neurons which were differentiated in vitro for 16, 25 and 35 days, respectively. Of these, neurons at day 25 were identified as most suitable for PD cell therapy while the other 2 cell types were less capable of producing functional recovery.[17]

These findings provide valuable guidelines to standardise the differentiation stage of transplantable cells used to treat PD. To better quantify the quality of transplantable DA neurons, one should perform a longitudinal assessment of the efficacy of transplanted mDA neurons using various neuroimaging modalities such as magnetic resonance imaging, magnetic resonance spectroscopy and positron emission tomography (PET) as well as behavioural measurement several months post-transplantation. It is possible that PET is able to better quantify the quality of transplantable mDA neurons using specific ligands before the cells can be used in clinical trials. It is therefore likely that molecular neuroimaging will play a major role in neurotransplantation research.

A major challenge in cell therapy in PD is identification of the discordance between satisfactory survival of transplanted cells and clinical improvement in some patients.[18] Certain confounders like ageing, disease progression, metabolic condition and mental health may affect axon sprouting and synaptic formation of grafted cells or postsynaptic efficacy of the host brain. These confounders may modulate the response to cell transplantation therapy. Identification of these confounders will greatly help clinicians to better stratify PD patients who are to be treated with cell transplantation.

Besides the therapeutic values of stem cell-derived cell transplantation, stem cell research also holds great promise by revolutionising the investigation of the aetiology of PD. Taking advantage of cutting-edge techniques such as human midbrain organoid generation and xenotransplantation, it is now feasible to re-examine the aetiology of PD in a multiple organ, polygenetic and human cell-based context. Human midbrain organoids can be generated from either healthy subjects or somatic cells (with mutation) of PD patients and then transplanted into a cavity created in the retrosplenial cortex of rodents.[19] Intracerebral implantation in rodents supports long-term survival and vascularisation of implanted organoids.[20] Many neuroimmunological features in PD—including blood brain barrier penetration of circulated immune cells in conditions of infection, innate microglia and astrocyte activation and gut-brain axis interaction—can be studied in this xenotransplantation platform.[21,22] Additionally, the interaction between genetic and environmental factors in PD pathogenesis can be investigated using this novel platform.

Currently, several trials that test DA neuron transplantation in PD patients are ongoing. A clinical trial that uses GMP (good manufacturing practice) grade DA cells derived from stem cells to treat PD patients is being funded by TRANSEURO.[23] Likewise, NYSTEM is supporting Lorenz Studer and Viviane Tabar of Memorial Sloan Kettering in New York for their work in this area (https://www.mskcc.org/research-areas/programs-centers/newyork-state-stem-cell-science-consortia).[24] The first clinical transplantation trial using iPSC began in Japan in 2018 and to date 1 patient has undergone neurotransplantation.[25] In Australia, a clinical trial that uses parthenogenetic stem cells (from chemically-induced unfertilised oocytes) as starting materials has been initiated. Parthenogenetic stem cells are rather attractive since they have fewer ethical issues, a lower number of de novo mutations (compared to iPSC) and apparently low immunogenicity. A summary of the unpublished preliminary findings (available online at https://www.globenewswire.com/news-release/2018/11/05/1645106/0/en/International-Stem-Cell-Corporation-Announces-Positive-Top-Line-Preliminary-Results-from-Parkinson-s-Disease-Clinical-Trial.html) seems to suggest the absence of any major safety issues to date.

There is considerable excitement over the prospect that human stem cell-derived DA neuron transplantation may usher in a new era in PD therapy. However, a lot will depend on the outcomes of ongoing clinical trials and subsequent validation of their findings and results through randomised controlled trials. At this stage, it is too early to draw any definitive conclusions while we wait with cautious optimism.

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