Review article

Cell replacement therapy in Parkinson’s disease

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With an ageing population, the incidence of Parkinson’s disease is increasing. The disease has an overwhelming impact on those it affects and has a limited repertoire of drug therapies available, each with problematic side effects. Stem cell therapy is an exciting prospect in the treatment of several neurodegenerative conditions. This article takes an in depth look at the great potential of cell replacement therapy for Parkinson’s disease, providing supporting evidence for investment in this potential treatment. After considering the basis for cell replacement therapy, the article looks at stem cells of different origins, summing up the strengths and limitations of each in relation to Parkinson’s disease. In addition to highlighting the cell replacement therapies available, the article also provides a chronology of research into this emerging field over the last 30 years.

Key words: Parkinson’s disease, stem cells, cell replacement therapy, stem cell transplant, regeneration, clinical trials

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Introduction

In 1984, Muhammad Ali, the former heavyweight champion of the world, was diagnosed with Parkinson’s disease (PD); he began to experience tremors and a slowness in his movements, known as bradykinesia. After years of battling with the disease, Ali now has difficulty speaking and coordinating his movements but remains an inspiration to many (The Guardian, 2009; Tim Dahlberg, The Seattle Times, 2012). PD affects around 6.3 million people worldwide, with most diagnoses being made over the age of 60. It is currently an incurable disease associated with irreversible loss of the dopaminergic neurons in the substantia nigra (SN) and striatum, which are structures of the basal ganglia, essential for fine motor control and initiation of movement (Barker, Cicchetti and Neal, 2012). As the central nervous system (CNS) has a limited capacity to regenerate its neurons, this has a devastating effect on motor function. Consequently, the four hallmark symptoms of PD are rigidity, tremor at rest, bradykinesia and postural instability. Current drug therapies target symptom management, and at present there are no cures for PD. This begs the question, is there potential for a treatment in the future and how does cell replacement therapy fit into the picture?

What is PD?

In 1817 James Parkinson documented six cases he had been observing in ‘An Essay on The Shaking Palsy’, describing the classic motor symptoms of the disease that now bears his name and establishing it as a medical condition (Parkinson, 1817). Today there is a greater understanding of the underlying causes of these symptoms. However, what triggers degeneration of the dopaminergic neurons in the first place remains unknown. Only 5% of PD cases can be attributed to specific heritable genes such as PARK1, a gene responsible for encoding the neural protein α-synuclein (Dawson and Dawson, 2003), the remaining 95% are idiopathic. Diagnosis of PD is still a clinical diagnosis based on the four cardinal symptoms, as there is no definitive test. Symptoms become apparent once over 80% of the dopaminergic neurons have been lost (Miller and O’Callaghan, 2014). On post-mortem examination, the SN of PD patients has a pale appearance. This is because dopaminergic neurons are rich in neuromelanin, the substance that gives rise to the dark pigmentation of the SN in normal adults (Zecca et al., 2003). Under a microscope abnormal aggregates of protein can be seen, known as Lewy bodies. The specific cause of idiopathic PD is uncertain, it is likely to be a combination of genetic and environment influences.
For instance, MPTP exposure, a compound initially synthesized as a narcotic, induces symptoms of PD. This demonstrates the potential of environmental toxins having a role and has provided one of the principal animal models of PD (Sian et al., 1999). The two leading theories for the pathogenesis of PD centre around the aggregation of misfolded proteins (such as α-synuclein) and oxidative stress caused by mitochondrial dysfunction (Dauer and Przedborski, 2003).

**Current drug therapy**

As PD is caused by a loss of the dopaminergic neurons, the main drug therapies focus on replenishing the dopamine within the basal ganglia. By replacing the dopamine, motor symptoms are reduced, and this has a significant impact on patients’ quality of life. Dopamine precursors such as L-DOPA and dopamine agonists form the basis of current therapy. L-DOPA is augmented with a DOPA decarboxylase inhibitor to reduce peripheral conversion, ensuring the majority of L-DOPA is converted to dopamine within the CNS (Poewe and Antonini, 2014). Monoamine oxidase B inhibitors can also be prescribed to reduce the breakdown of dopamine within the brain. While these drugs initially relieve patients of their symptoms, their therapeutic benefit diminishes with time. This is known as ‘wearing off’ and means patients require a higher dose to experience the same benefit (Stocchi, 2006). Unfortunately, these drugs also have unpleasant side effects such as dyskinesia, which is the occurrence of involuntary movements. Although medication is the mainstay of PD management, there are alternative treatments such as speech and language therapy or surgical options such as deep brain stimulation (DBS) (Odekerken et al., 2013). Current therapies have their limitations as they focus on symptomatic relief only and do nothing to reverse or slow down the progression of the disease. As PD is caused by degeneration of dopaminergic neurons, it stands to reason that differentiated stem cells could be implanted to replace lost neurons and consequently re-innervate the striatum.

**The case for cell replacement therapy**

Cell replacement therapy is a promising avenue into the investigation and treatment of neurodegenerative diseases. The CNS is unable to regenerate its own neurons, due to the physical and chemical barriers formed by glial scars (Ohtake and Li, 2014). Stem cells have the ability to multiply and differentiate down any cell line, this is known as pluripotency. Current research is focussing on the pluripotent potential of various forms of stem cells. By inducing stem cells to differentiate under the correct conditions, dopaminergic neurons can be created. These neurons can be transplanted into a patient with PD, replacing their dopamine levels and providing symptomatic relief. Both the Michael J Fox Foundation and Parkinson’s UK refer to stem cell therapies on their websites and actively back research into this potential therapy.

The idea of treating PD using cell replacement therapy is not a new one; research in this area started in the early 1990s. Studies investigating the effects of foetal neuronal tissue in PD patients yielded promising results. A study published in 1994, transplanted foetal ventral mesencephalic tissue (which would later develop into the basal ganglia) rich in dopaminergic neuroblasts (precursors) from aborted foetuses into the striatum of two patients with idiopathic PD (Peschanski et al., 1994). The team followed up the patients and compared PET scan data of Flurodopa (dopamine with a radioactive isotope) with motor changes. The results showed an increase in Flurodopa uptake at the site of grafting along with improved motor performance in both patients. This study demonstrated that neural transplantation was a possibility and was a step in the right direction for cell replacement therapy; it showed that transplanted dopaminergic neurons could survive and re-innervate the striatum. A number of studies reached the same conclusions, adding strength to the potential of cell replacement therapy as a treatment for PD (Hoffer et al., 1992; Defer et al., 1996; Levivier et al., 1997).

These studies also demonstrated some of the limitations with transplantation of foetal tissue. One study retrospectively followed up 14 patients who had received a graft of foetal mesencephalic tissue; the results showed that a number of subjects suffered from graft-induced dyskinesias (Hagell et al., 2002). The mechanism behind this was not fully understood, although it was hypothesized that the side effects could be due to dopamine reaching over-sensitized receptors or due to the non-dopaminergic portions of the graft. It must also be appreciated that while these transplants demonstrated the promising potential of cell replacement therapy, it is not a clinically viable model to use foetal tissue to treat PD patients. It would be ethically questionable to use aborted foetal tissue as a treatment and require more than can be realistically sourced.

**Embryonic stem cells**

Following the encouraging results of foetal tissue grafts, embryonic stem cells (ESCs) became the focus of research into cell replacement therapy. Stem cells could provide the perfect source for neuronal replacement; ESCs are derived from the inner cell mass of the blastocyst and are pluripotent with the ability to proliferate extensively.

A study looking at the effect of transplanting a low dose of mouse ESCs to OHDA-lesioned (neurotoxic compound which targets dopaminergic neurons) rats showed that the naive cells developed into functional dopaminergic neurons in some cases (Bjorklund et al., 2002). Using PET scans and quantitative measurements of rotational behaviour in response to amphetamines, rats with ESC-derived dopaminergic neurons showed some gradual but significant improvement of symptoms. However, this study also highlighted some unfavourable side effects. The study had a high rate of tumour formation and graft failure. Of the 25 rats that
received the transplants, 6 showed no ESC survival and 5 died of teratoma-like tumours (Bjorklund et al., 2002). While the study yielded some positive results, the high incidence of tumour formation indicates some of the risks involved in transplanting highly proliferative tissues.

Another study published in Nature followed a similar procedure; here they looked at stimulating the differentiation of ESCs into dopaminergic neurons in vitro before transplanting these into an animal model of PD (Kim et al., 2002). The results showed that the grafted ESC-derived neurons survived and proved to be functional. However, the study agreed that tumour formation was an unacceptable complication associated with ESC grafts and that further animal studies were required to understand the safety and efficacy of these transplants.

Recent studies have since had mixed results in animal models. However, improvements in culture methods and differentiation protocol have succeeded in creating a more homogenous and scalable population of dopaminergic neurons (A9-type) specific to the ventrolateral and caudal regions of the SN. Animal models have subsequently seen improved outcomes, which correlates with evidence of increased fibre outgrowth. Although, there is still concern as to the potential for aberrant inervation and graft-induced dyskinesias remains unknown. It is hypothesized that genetic modification of these implanted neurons might be able to limit excessive outgrowth (Ambasudhan et al., 2014). A number of techniques have been suggested to minimize the risk of tumour formation; these include prolonged pre-differentiation of ESCs, selection of differentiated cells for transplantation and genetic engineering to block tumourigenic pathways (Ambasudhan et al., 2014).

The potential therapeutic use of ESCs and the possible complications are clearly demonstrated by these studies. As with foetal tissue implants mentioned earlier, they hint towards the intriguing potential for a method of regenerating lost dopaminergic neurons in PD patients. Unfortunately, they also demonstrate how far cell replacement therapy is from being an operational procedure for PD patients. As with tissue implants, similar limitations apply. Both models require immunosuppression to prevent graft rejection, and ESC transplants are associated with tumour formation. Supply of ESCs is also limited and once again poses complicated ethical questions.

### Adult stem cells

While ESCs provide promise for the future of PD treatment, as a basis for cell replacement therapy the resources are limited. Interestingly, it has been discovered that adults also have regions of undifferentiated, self-renewing stem cells. For instance, haematopoietic cells found in bone marrow are precursors for all blood cell types in the body; these stem cells have been used successfully in transplants for years. Therefore, it would seem reasonable to believe that native neural stem cells, found in the subventricular zone and hippocampus, could be used in a similar way (Clarke et al., 2000). By implanting these neural stem cells (NSCs) into the striatum of PD patients, extracellular signalling might influence their differentiation and form dopaminergic neurons.

A study conducted in 2002 implanted NSCs unilaterally into MPTP-treated mice (animal PD model). Following this, it was observed that some mice began rotating in the opposite direction to the implantation. An amphetamine challenge (causing DA release) and later histological evidence were used to confirm that this was due to the implanted NSCs. Although it was found that some of the transplanted cells differentiated into dopaminergic neurons, surprisingly it was discovered that the majority of the dopaminergic neurons present were ‘rescued’ host cells (Ourednik et al., 2002). It was hypothesized that NSCs have an intrinsic ability to produce trophic (survival/growth) and neuroprotective factors sufficient to save damaged cells. The study demonstrated that NSCs migrated readily throughout the striatum, particularly in the aged brain; here they were able to differentiate into dopaminergic neurons in response to host signals. In addition, it showed the potential of NSCs to influence the existing CNS, rescuing the present neurons and recovering the striatal dopaminergic system (Ourednik et al., 2002).

It is worth noting that adult stem cells can be derived from sources other than the brain, which requires an invasive biopsy. For instance, studies have demonstrated that stem cells can be harvested from the oral mucosa, endometrium, bone marrow and adipose tissue. Given appropriate in vitro signalling, these cells have the potential to differentiate into dopaminergic neurons and have also proven to be effective when implanted into animal models of PD (Berg et al., 2014; Ganz et al., 2014; Wolff et al., 2015).

This demonstrates the promising advantages of adult stem cells compared with ESCs. Alongside showing similar regenerative potential in early trials, adult stem cells could be extensively cultured and potentially stimulated to differentiate in vitro. Another benefit of adult stem cells is that it does not depend on aborted foetal tissue, making it less ethically ambiguous, it also means there is a readily available self-derived source. It seems reasonable that with an appropriate method, stem cells could be harvested, cultured, treated and subsequently implanted into the striatum, overcoming the issue of graft rejection.

This potential therapy was carried out on Mr Dennis Turner in the USA: after suffering from PD for 14 years and experiencing severe symptoms, he received a transplant of his own NSCs that had been cultured and matured into dopaminergic neurons from cortical tissues (Lévesque, Neuman and Rezak, 2009). Mr Turner testified at a US Senate Committee meeting in 2004 (Congressional Record, 2007) as an advocate for the funding of research into treating PD using cell replacement therapy. In part of his testimony he stated ‘I have no doubt that because of this treatment I’ve enjoyed five
years of quality life that I feared had passed me by’. This powerful account shows the difference this treatment made to an individual who feels that others should be allowed to experience the benefit of cell-based therapies. Two years later in July 2006 President George Bush vetoed the Stem Cell Research Enhancement Act of 2005, demonstrating that the obstacles faced by stem cell research are also political and a greater public understanding is necessary for continuing advancements in this field.

**Induced pluripotent stem cells**

Although NSCs showed some promise they proved to be far from perfect, requiring invasive biopsies and only aiding in neuronal survival. In 2006, a research group in Japan led by Shinya Yamanaka (Takahashi and Yamanaka, 2006) devised a method of deriving pluripotent cells from adult mouse fibroblasts. Put simply, by expressing transcription factor (TF) genes for Oct4, Sox2, Klf4 and c-Myc cells obtained the pluripotent characteristics of ESCs, these cells were termed induced pluripotent stem cells (iPSCs). In the years following this study, similar techniques were used to produce iPSCs from human cells. This offered an exciting new avenue for stem cell research by circumventing the ethical dilemmas previously associated with ESC research, while also providing cells with an unhindered ability to differentiate down cell lineages. Animal studies that followed show that dopaminergic neurons derived from iPSCs improve motor symptoms in PD model rats (Wernig et al., 2008). As well as providing a potential source for transplantation, iPSCs derived from PD patients could be paramount to modelling the disease in vitro aiding the advance of drug therapies (Fig. 1).

As with adult stem cells, iPSCs eliminate the need for immunosuppression by having a patient-derived cell source.

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**Figure 1.** Life cycle demonstrating the potential sources of induced pluripotent stem cells and the applications for cell replacement therapy or cellular modelling of Parkinson’s disease. (Reproduced from Brandl et al., (2014). © 2015 International Parkinson and Movement Disorder Society, with permission from John Wiley and Sons).
iPSCs also avoid the ethical issues associated with ESCs; however, they do come with their own set of limitations. As viral vectors are used to integrate the TF genes, they can also randomly integrate elsewhere in the genome and modify cells further. These TF genes also have oncogenic potential as their increased expression could induce tumour formation, as was found in the PD model rats (Wernig et al., 2008). To overcome this, it has been proposed that different methods be used to increase expression of these TFs other than introducing DNA fragments (Yee, 2010). More recent studies have shown that mRNA can be implanted directly into cells without genetic alteration; it is also possible to use DNA-based vectors that are less likely to integrate into host genes (Brandl et al., 2014). It is apparent that with all of the discussed potential cell therapies, there is need for further research into their safety and efficacy to determine whether they could ever form the basis of a viable treatment for patients with PD.

What does this mean for cell replacement therapy?

Studies have established that transplants survive and become established within the striatum, improving dopaminergic delivery to the surrounding structures, aiding in fine motor control and therefore abating the most debilitating symptom of PD. This has been demonstrated not only with improvements in animal and human models but also with PET scan data showing Flurodopa uptake at graft sites.

Therefore, would it be correct to assume a cell replacement therapy will be readily available in the foreseeable future? It is important that the current limiting factors of cell replacement therapy are taken into account. While studies have shown a reduction in motor symptoms, increased dopaminergic innervation does not affect the non-motor symptoms of PD such as fatigue, depression, hallucinations and mood swings. This is believed to be due to continued degeneration of serotonergic projections to the brain regions controlling sleep, feeding and emotion (Politis et al., 2012). Some evidence has also emerged that the disease spreads from host cells to grafts, meaning transplants could eventually degenerate anyway causing a recurrence of symptoms (Li et al., 2008). However, as PD is a late-onset slow-progressing degenerative disease, it can be argued that grafts will last a patients’ lifetime or at least provide relief for a significant portion. It can also be argued that while these grafts may not tackle the entire range of PD symptoms, grafts go a long way to relieving the most severe symptom, allowing patients to regain some level of function and an increased quality of life.

Conclusion

In light of all the evidence discussed within this article, a cell-based treatment for PD has great potential and should be actively sought. Implants into animal models of PD and a number of human grafts have proved to be effective in reducing the cardinal motor symptoms of PD. It is necessary for
larger clinical trials to take place to gain an appreciation for the effectiveness of cell-based therapies compared with the current pharmacological gold standard. Patients undergoing surgery for DBS implantation would be a sensible population for a clinical trial. Individuals suitable for DBS already meet a number of the criteria for biological studies. In addition, these patients already require a surgical intervention and so it would remove the need for sham surgical procedures, see Fig. 2 (Rowland et al., 2014). Knowledge gleaned from larger studies will make a valuable contribution to the field and encourage the development of cell therapies for other neurodegenerative conditions. Although replacing dopaminergic neurons does not tackle the non-motor symptoms of PD, a stepwise approach to cell-based therapies is necessary. Future innovations may be able to provide a wider spectrum of symptom relief. These implants alleviate the most debilitating symptoms of PD and last long enough to significantly improve patient’s quality of life. With recent improvements in both the safety profile and results demonstrated by cell-based therapies, continued investment in future studies is justified.

**Author’s biography**

Tom is currently in his 5th year reading Medicine at Imperial College London. Last year he undertook a BSc in Neuroscience and Mental Health to further his understanding of this fascinating and rapidly evolving field of medicine. Following the BSc, Tom is now strongly considering research as a future prospect alongside his clinical studies. Studying Neuroscience has proved to further Tom’s interest; it stands out as a discipline of medicine he finds both challenging and thoroughly enjoyable. Tom endeavors to pursue his interest in this field over the coming years and hopes to attain an Academic Foundation Programme job with a Neurology rotation, allowing him to partake in clinical medicine as well as developing skills in research and teaching.

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