STEM CELLS AND PARKINSON’S DISEASE

BY
MAHA NAZIR

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK AND VET-MEDLINK 2014

Grade awarded: Pass with Merit
ABSTRACT

Stem cell research has drastically progressed in recent years, with these totipotent cells being recognised as the key to curing several currently incurable conditions. Whilst such research is predominately utilising embryonic stem cells, the barrier of ethics is still a major concern hence the development of induced pluripotent cells – ‘man-made’ stem cells – used alongside embryonic stem cell research. These remarkable cells are becoming a popular choice for future treatment of neurodegenerative diseases, such as Parkinson's disease. Being the second most common neurodegenerative disorder after Alzheimer's disease, Parkinson’s affects 0.7% of the elderly population and with an increasing ageing population a solution is desperately needed. In this paper I will explore current research in this field and will conclude that the benefits of stem cells may extend beyond treatment forms towards hopes of developing preventative measures.

INTRODUCTION

Stem cells are a class of undifferentiated cells with the potential to develop into any somatic body cell. They are therefore said to be pluripotent, a term that denotes their ability to give rise to almost all cell types. These renewable cells are derived mainly from two sources: embryos or adult tissues. Adult – or somatic – stem cells exist after embryonic development and are found throughout the body within different tissue types such as brain tissue, bone marrow and skin. These stem cells have the ability to self-renew indefinitely thus enabling them to generate a range of cell types. However, adult stem cells are limited in their ability to differentiate and cannot extend beyond their tissue of origin, hence being termed as multipotent cells.

Embryonic Stem Cells (ESCs) can be extracted from blastocysts or from the umbilical chord. A blastocyst is a group of thirty two to sixty four cells formed four or five days after fertilisation of the
egg and sperm. The cells derived from the blastocyst itself are usually obtained from the discarded embryos of In Vitro Fertilisation. The structure of a blastocyst is such that there is an inner cell mass (embryoblast) and an outer cell mass (trophoblast); it is the embryoblast that is the source of the totipotent ESCs that will have the total potential to differentiate and become all cell types of an adult organism (Fig. 1).

![Fig. 1](image_url)

Stem cell research itself is relatively young, with the first mice embryonic stem cells identified and cultivated in 1981 by Martin Evans, at the University of Cambridge. The first isolation of cells from the inner cell mass of early embryos was by Thompson, of the University of Wisconsin, in 1998, to develop the first stem cell line. During that period, probably the most well-known and controversial utilisation of stem cells was carried out with the birth of Dolly, a cloned sheep, using somatic cell nuclear transfer in 1997 at The Rosalind Institute.

These remarkable cells’ abilities have been recognised within the medical world and can now be seen as having unlocked potential for development into breakthrough treatments for both currently curable and incurable conditions, including various cancers.

One such illness is Parkinson’s disease. Parkinson’s disease is a neurological disorder that affects one in every five hundred people in the UK, with sufferers usually being over the age of fifty. With an increasing aging population in the UK, the escalating number of sufferers of the disease is becoming a major concern for healthcare professionals and researchers. The disease targets and kills dopamine-producing neurons in the part of the brain known as the Substantia Nigra (Fig. 2).
Dopamine is a neurotransmitter, a chemical that plays a critical role in the way our brain controls movement. Dopamine disorders in the frontal lobe can cause a decline in several neurocognitive functions, for example memory, attention and problem-solving. As the dopamine producing nerve cells die, Parkinson’s patients develop tremors and rigidity, whilst their movements slow down. Other common symptoms include: loss of sense of smell, sleep disorders, depression and constipation. The degeneration can spread to other nerve cells and lead to Lewy body dementia in the later stages of the disease (Başar Bilgiç et al. 2013). Despite the prevalence of the disease, scientists are still baffled as to what specifically causes Parkinson's disease. In about one in twenty cases, it is thought to be caused by an inherited dysfunction in the production of a protein, alpha-synuclein protein; the cause of the remaining 95% of cases remains unclear.

Despite the lack of clarity regarding the underlying cause of Parkinson's disease, we are aware of the cells and areas of the brain involved. Consequently, as a single well-defined type of cell is affected, we are provided with substantial reasons to develop treatments that replace the lost nerve cells with healthy new ones; this form of breakthrough research is being carried out at Lund University in Sweden. However, transplantation is not the sole application of the stem cell research. Scientists could also use stem cells to study the mechanism of Parkinson’s disease and test substances that could be developed into new forms of diagnostic methods.

**DISCUSSION**

Stem cell research in relation to Parkinson’s disease is relatively recent, yet promising development is being achieved.
A European research group based at Lund University, Sweden (Parmar et al. 2014) used a rat model to test the effect of embryonic stem cells engineered to produce the neurotransmitter dopamine. To form the rat model, the researchers destroyed the dopamine cells in part of the rat’s brain and replaced them with human embryonic stem cells. Pre-transplantation, the rats were assessed by PET scans for deficits in striatal dopaminergic neurotransmission, using measures of D2/D3-receptor occupancy (Moon et al. 2010) and 18F-LBT999 as a tracer for the dopamine transporter (Dollé et al. 2007). In the DA-denervated striatum of the rats, binding of the measures was significantly increased, signifying a profound reduction in dopamine release. The researchers then transplanted hESC-derived dopamine producing neurons to the striatum of the basal ganglia. The grafted rats were followed by MRI and PET scans (Fig. 3) up to six months after transplantation, the point at which grafts started to become functional (Piccini et al. 2000).

Serial MRI imaging showed an increase in volume from one to five months post-transplantation, indicating maturation of the transplanted cells. Five months post grafting also revealed a high content of the acid N-acetylaspartic within the transplanted area, which indicates a successful graft uptake. After grafting, binding to receptors was normalised to intact levels, indicating successful active release of dopamine from the transplanted neurons. Similarly, the near-complete loss of dopamine transporter binding was reversed to around 50% of normal levels.

It was found that the new cells showed all the properties and functions of the dopamine producing neurons lost in Parkinson's disease. The research supports the ESCs’ functional efficacy and capacity for long-distance reinnervation, which is predictive of their therapeutic potential in humans. Parmar noted that the cells survived in the long term and restored production of dopamine in the brain, functioning in a similar way to dopamine cells of the human fetal midbrain.
"This study shows that we can now produce fully functioning dopamine neurons from stem cells. These cells have the same ability as the brain’s normal dopamine cells to not only reach but also to connect to their target area over longer distances. This has been our goal for some time, and the next step is to produce the same cells under the necessary regulations for human use. Our hope is that they are ready for clinical studies in about three years." - Malin Parmar (Lead Researcher, Lund University, Sweden)

Parmar’s team are currently working in conjunction with other European pre-clinical researchers, looking into fetal human dopamine transplants and their correlated side effects of the graft-induced movements provided (Transeuro).

Whilst the study carried out by Parmar et al. (2014) was successful in its own merit, the overwhelming ethical issues related to the usage of embryonic stem cells in research poses a dilemma for future development. Obtaining embryonic stem cells involves destruction of the early embryo; this means destroying a potential human life. This is the major issue that has to be balanced with the view that such research could lead to the discovery of new medical treatments that would alleviate the suffering of many individuals. The consensus enshrined in the Human Fertilisation and Embryology Act in 1990, is that “the embryo does have moral rights but not to the same extent as a living person”. This has allowed the progression of research on these stem cells. The source of embryonic stem cells is also an issue as the stem cells can only be extracted from aborted foetuses or those discarded from IVF, which poses both moral and religious problems. This issue could be resolved by the use of somatic adult stem cells, however these cells are already differentiated and do not contain as much unlocked potential as their embryonic counterpart; this is problematic in developing the specific dopamine producing neurons required to treat Parkinson’s disease. Therefore, the use of stem cells retrieved from the umbilical cord rather than the blastocyst itself or the use of Induced Pluripotent Stem (iPS) cells are currently being developed.

After birth, blood left in the umbilical cord is rich with totipotent haematopoietic (blood) stem cells (HSCs) that are relatively easy to collect, without posing risk to the mother or baby. This resolves the risk to the foetus and is also a method to utilise such cells that would normally be regarded as waste. Unfortunately, this process is not flawless, with the main disadvantage of using umbilical cord blood being that the volume available is fixed and relatively small. Therefore, the number of stem cells available for transplantation is low compared to the number of cells that can be collected through ESCs.

On the other hand, in cohesion with research into the treatment of Parkinson’s disease, stem cells are being used in the development of diagnostic tools to evaluate genetic and environmental factors implicated in the disease. Such cells are known as induced pluripotent stem cells. iPS cells – discovered in 2007 – provide a promising solution to the problems highlighted earlier. These cells are essentially ‘man-made’ stem cells that possess the ability to differentiate into other cell types. iPS cells are obtained from mature cells, for example skin cells, which are then reprogrammed into an embryonic-like stem cell state. As mentioned in the introduction, we are still not certain of the specific cause of Parkinson’s disease and therefore the majority of research is being carried out to develop therapies that can treat the damage caused by the disease. However, an exciting future prospect of stem cells research is that scientists could use cells of Parkinson’s patients to create iPS cell models with the same intrinsic cellular machinery of a Parkinson’s patient. This will allow scientists to better understand the initial causes of the disease and will hence allow us to develop
preventative methods rather than just replacements of the damage already caused. This will have to be carried out in conjunction with genetic research if a diagnostic tool is to be developed.

Whilst the study by Parmar et al. (2014) showed promise in the use of stem cells in rats, it is important to realise that the investigation involved the use of animals and laboratory controlled settings. Questions are posed as to how realistic these prospects are in human clinical treatments. Such trials are ongoing, with the following study by Kefalopoulou et al. (2014) showing the long-term outcome of two patients with Parkinson’s disease who received human fetal ventral mesencephalic neural grafts to demonstrate the magnitude and duration of the therapeutic effect that is a result of a cell replacement strategy. The researchers stated: “such long-term follow-up data can usefully inform on the potential efficacy of this approach, as well as the design of trials for its further evaluation”. Clinical assessments were performed eighteen and fifteen years post-transplantation and it was found that motor improvements were sustained over the years. Despite each patient suffering Parkinsonism for thirty years prior to the study, with troublesome fluctuations and dyskinesias (involuntary muscle movements), both patients now present very mild symptoms (Fig. 4) and are consequently independent of any pharmacological dopaminergic drug treatments for over a decade.

Figure 4 shows the follow up results of one of the patients using the UPDRS, Unified Parkinson’s Disease Rating Scale (Hoehn and Yahr 1967) as a rating tool that follows the longitudinal course of Parkinson's disease. The UPDRS involves a severity evaluation by interview, and consists of 3 sections:
1) Mentation, Behaviour and Mood
2) Activities of Daily Life
3) Motor sections
As seen in Figure 4, the graft treatment is shown to be successful. As time passes, the UPDRS score decreases, showing the reduced severity of motor symptoms. However in the report published by Kefalopoulou et al. (2014), the researchers are fully aware of the lack of a representative sample as only two individuals representing particularly successful cases are investigated; they warn that any conclusions should be drawn with caution. Nevertheless, the research does provide support that dopaminergic cell transplantation may offer “a substantial and very long-lasting compensatory effect in Parkinson’s disease”. Hence, encouragement is provided for basic science and clinical studies striving to develop clinically competitive stem cell-based dopaminergic cell therapies for future treatment of Parkinson’s disease.

There have been promising developments in animal models regarding the feasibility of using stem cells as part of treatments for Parkinson’s disease. However, several questions are yet to be answered regarding such treatments in humans. We do know how to collect the stem cells and direct them into the correct structure for use, but how can these cells be physically transplanted into humans? Is it a matter of direct injection of cells into the basal ganglion; if this is so then are we aware of how this will affect other parts of the brain? Or can the stem cells be transported via the blood and be deposited at the necessary part of the brain? These are the questions that indicate need for further research and consideration into the logistics of such treatments.

CONCLUSION

Stem cells are totipotent cells of adult or embryonic nature used in treatment of several conditions. This paper highlights breakthroughs in recent years both in animal models and clinical trials about using stem cells as a treatment modality in Parkinson’s disease.

Though this mode of therapy is very promising, it is in the early stages of development and can presently be seen as idealistic, as the moral and ethical dilemmas involving embryonic stem cells are yet to be resolved. Further clinical research is also needed with regards to the mode of a safe and effective delivery method of the stem cells to the target region in the brain.

I believe further basic research into the potential of induced pluripotent cells needs to be explored so that we can develop a preventative method of dealing with Parkinson’s disease. Currently, funding for research is primarily directed towards therapies to reverse the damage already caused by the loss of dopamine producing neurons. However, by expanding the research of iPS cells – that allow us to reproduce diseased cells – we will be able to explore how Parkinson’s disease is initially caused and thus develop ways to prevent the underlying neurodegeneration. This allows for pre-emptive measures rather that therapeutic, which in the long run will prove more economical for the Nation Health Service in the UK’s currently ageing population.
REFERENCES

Dopamine Neurons Show Similar Preclinical Efficacy and Potency to Fetal Neurons when Grafted in a Rat Model of Parkinson’s Disease, Shane Grealish, et al., Cell Stem Cell, doi:10.1016/j.stem.2014.09.017
(Including Fig. 3)


(Fig. 1) WIKIMEDIA. Image of Blastocyst Structure. [Online] Available from: http://upload.wikimedia.org/wikipedia/commons/f/fd/Blastocyst.png

(Fig. 2) NEUROSCIENCE NEWS. Image of a Parkinson’s Disease Sufferer’s Brain. [Online] Available from: http://neuroscienccenews.com/pink1-parkin-neurodegeneration-parkinsons-903/parkinsons-disease-brain-differences/

(Including Fig. 4)

MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL. Hoehn and Yahr Staging of Parkinson's Disease, Unified Parkinson Disease Rating Scale (UPDRS), and Schwab and England Activities of Daily Living. [Online] Available from:
http://neurosurgery.mgh.harvard.edu/functional/pdstages.htm

MEDICAL NEWS TODAY. What are Stem Cells? [Online] Available from:
http://www.medicalnewstoday.com/info/stem_cell/

NEW SCIENTIST. Stem cell timeline: The history of a medical sensation. [Online] Available from:

PSYCHOLOGIST WORLD MAGAZINE. Dopamine Neurotransmitter. [Online] Available from:

THE MICHAEL J.FOX FOUNDATION FOR PARKINSON’S RESEARCH. Stem Cells and Parkinson’s Disease. [Online] Available from: