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A REVIEW OF STEM CELL THERAPY FOR MANAGEMENT OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease (PD) is a common neurodegeneration disorder. While a number of non-motor manifestations arise, the typical clinical features involve a movement disorder consisting of bradykinesia, resting tremor, and rigidity, with postural instability occurring at a later stage. There is no disease modifying treatments, and management is centered on symptom control using primarily dopaminergic drugs. While effective at improving the motor symptoms of PD, these treatments result in significant adverse effects, due to non targeted and non physiological delivery of dopamine to the brain. In this review we will discuss the how to reconstruct nigro-striatal neuronal pathways using dopaminergic neurons and targeting by cell based therapy to overcome adverse effects of traditional treatment.

KEY WORDS: Parkinson's disease, stem cell, cell based therapy, regeneration therapy.

INTRODUCTION

Parkinson's disease is a progressive neurological disorder. The first signs are problems with movement. Smooth and coordinated muscle movements of the body are made possibly by a substance in the brain called dopamine. Dopamine is produced in a part of the brain called the "substantia nigra". In Parkinson's the cells of the substantia nigra start to die. When his happens, dopamine levels are reduced. When they have dropped 60 to 80 percent, symptoms of PD start to appear. There's currently no cure for PD which is chronic and worsens over time. More than 50k new cases are reported in the United States each year. But there may be even more, since Parkinson's is often misdiagnosed. Parkinson's symptoms usually begin gradually and get worse over time. As the disease progresses, people may have difficulty walking and talking. They may also have mental and behavioral changes, sleep problems, depression, memory difficulties, and fatigue. This section we will discusses some of the stem cell approaches that are being investigated as a potential means of doing this and where they may fit in the future site of PD management.[1,2]

HISTORY OF CELL BASED THERAPIES FOR PARKINSON'S DISEASE[3, 4]

1980 – Transplanted rat fetal ventromedial (VM) tissue functions in hydroxydopamine rats.
1988 – Human fetal VM transplanted into 2 PD patients
1992 – Two PD patients respond to human fetal VM
1998 – Transplanted mouse embryonic stem cells (ESCs) differentiate to DA neurons
2005 – DA Neurons identified in VM PD patients
2006 – Directed differentiation of human ESCs to functional DA neurons
2010 – PD Patient induced pluripotent stem cell (ipsc) differentiate to functional DA neurons
2015 – Successful human ipsc transplant in primates
2018 – First ipsc clinical trial for PD

AIM OF STEM CELLS USED IN PARKINSON'S TREATMENT

The aim of stem cell therapy for PD is to reconstruct nigro-striatal neuronal pathways using endogenous neural stem/precursor cells or grafted dopaminergic neurons. As an alternative, transplantation of stem cell derived dopaminergic neurons into the striatum has been attempted, with the aim of stimulating local shapes formation and /or release of dopamine and cytokines from grafted cells. Candidate stem cells include neural stem/precursor cells, embryonic stem cells and other stem/precursor cells. Among these, embryonic stem cells are pluripotent cells that proliferate extensively, making them a good potential donor source for transplantation. However, tumor formation and ethical issue present major problems for embryonic stem cell therapy. This review describes the current status of stem cell therapy for PD, as well as future research approaches from a clinical perspective.

Embryonic stem (ES) cells have been suggested as candidate therapeutic tools for cell replacement therapy in neurodegenerative disorders.[5, 6] However, limitations for the use of these cells lie in our restricted knowledge of the molecular mechanisms involved in their specialized differentiation and in the risk of tumor formation. Recent findings suggest that the EGF-CFC protein cripto is a key player in the signaling pathways controlling neural induction in ES cells. Here we show that *in vitro* differentiation of crypto ES cells results in increased dopaminergic differentiation and that, upon transplantation into Parkinson's rats; they result in behavioral and anatomical recovery with no tumor formation. The use of knockout ES cells that can generate dopamine cells while eliminating tumor risk holds enormous potential for cell replacement therapy in PD. [7]

- Neural stem cells (NSCs) from human fetal brain, expanded and differentiated to DA-ergic neurons
- Pluripotent cells generated from blastocytes (ESCs) or fibroblasts (iPSCs), expanded and differentiated to DA-ergic neurons
- DA-ergic neurons generated by direct conversion of fibroblasts
- Bone marrow-derived mesenchymal stem cells (MSCs)[8]

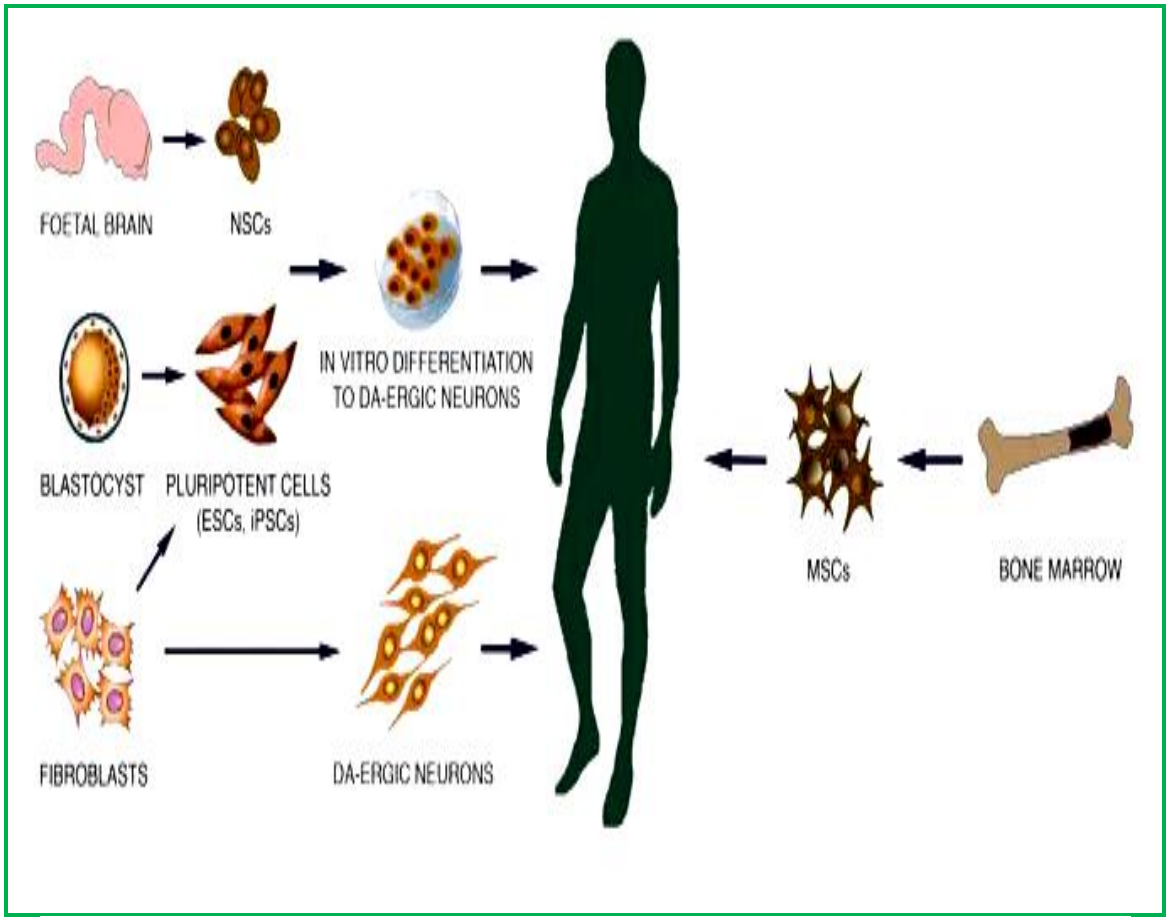

Fig. 1: Schematic illustration of possible sources of stem cells for therapy in Parkinson's disease.

Table 1: Sources of experimental cell based treatments for Parkinson's disease.

Cell types trialed in humans	Cell types with forthcoming trials in humans
Autografts Adrenal medullary cells Carotid body cells Mesenchymal stem cells **Allografts** Human fetal ventral mesencephalon Retinal pigment epithelial cells **Xenografts** Porcine ventral mesencephalon	Embryonic stem cell derived neural progenitors Induced pluripotent stem cell derived neutralprogenitors

Advantages and disadvantages of stem cell types used in parkinson's disease [9,10]

There are different types of stem cells are used in Parkinson's disease which contains some effects

Embryonic stem cell (ESCs)

Advantages

1. Highly proliferative/pluripotent
2. Able to form all three germ layer
3. Generate dopaminergic neurons
4. Transplantations survival/some degree of functional recovery

Disadvantages

1. Risk of tumour formation
2. Ethical issues
3. Genomic instability

Induced pluripotent stem cells (iPSCs)

Advantage

1. Unlimited PD patient-specific cells/autologous transplantation
2. Transplantation survival/some degree of functional recovery
3. Minimized immune reaction and ethical issues

Disadvantages

1. Risk of tumour formation
2. In autologous transplantation risk of susceptibility to the original
3. Pathology of the patient

Mesenchymal stem cells (MSCs)

Advantages

1. Improve motor performance in mice
2. No reported adverse effects in humans
3. A realistic cell source for regenerative medicine
4. Easily accessible from different tissues

Disadvantages

1. Modest clinical improvement in humans

Fetal brain neural stem cells (fNSCs)

Advantages

1. Lower risk of tumour formation and immune rejection in comparison with ESCs
2. Ability to differentiate into neurons, astrocytes, oligodendrocytes, and dopamine neurons

Disadvantages

1. Limited differentiation *in vivo*
2. Partial effect in PD-like symptoms
3. Risk of GIDs
4. Ethical issues
5. Histocompatibility concerns (f) limited supply

Although a number of stem cell types have been considered as potential treatment options for PD, the most promising are embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSC)

MECHANISM OF STEM CELL THERAPIES IN PARKINSON'S DISEASE [11]

The mechanism is classified in two ways it includes

- Direct Repair Pathway
- Indirect Repair Pathway

Direct repair pathway

It includes supplementing endogenous neurogenesis, DA neuron differentiation, DA release, striatum reinnervation and neural trails integration.

Indirect repair system through trophic factors

Stem cells express various neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), cerebral dopamine neurotrophic factor (CDNF), nerve growth factor (NGF), or glial-derived neurotrophic factor (GDNF), and facilitate DA neuronal differentiation and maintenance.

Human embryonic stem cells have been manipulated in the laboratory to produce a new generation of dopamine cells that behave like native dopamine cells when transplanted. Dopamine cells made from human embryonic stem cells are paving the way for a new treatment for Parkinson's.

EXPERIMENTAL RESEARCH[12]

Human embryonic stem cells have been manipulated in the laboratory to produce a new generation of dopamine cells that behave like native dopamine cells when transplanted. Dopamine cells made from human embryonic stem cells are paving the way for a new treatment for Parkinson's. Human embryonic stem cells (hESCs) have been proposed as a source of dopamine (DA) neurons for transplantation in Parkinson's disease (PD). Stem cells offer great promise as a therapy for Parkinson's disease, but numerous hurdles remain to be overcome with stem cell therapy. The adverse event profile of transplantation must be determined, and societal and ethical issues addressed. As Parkinson's disease involves degenerations of both dopaminergic and non-dopaminergic neurons, it also remains to be determined if transplantation of even the ideal dopamine neuron will improve non-dopaminergic features of the disease provide benefits superior to existing therapies.

Embryonic stem cell research is a promising field that has created political and ethical controversy. Scientists are currently developing a number of strategies for producing dopamine neurons from human stem cells in the laboratory for transplantation into humans with Parkinson's disease. The successful generation of an unlimited supply of dopamine neurons may offer hope for Parkinson's patients at some point in the future. Research currently being explored utilizes embryonic stem cells, which are undifferentiated cells derived from several day-old embryos. Most of these embryos are the product of in vitro fertilization efforts. Researchers believe that they may be able to prompt these cells,

which can theoretically be manipulated into a building block of any of the body's tissues, to replace those lost during the disease's progression. There is hope that adult stem cells, which are harvested from bone marrow, may be utilized in a similar way to achieve results. Fewer ethical questions surround this sort of research, but some experts believe that adult stem cells may be more difficult to work with than those from embryos. Either way, the scientific community is nearly unanimous in arguing that research efforts and potential breakthroughs will be negatively impacted if they are not allowed to work on both types of stem cells. Human studies of so-called neurotropic factors are also being explored. In animal studies, this family of proteins has revived dormant brain cells, caused them to produce dopamine, and prompted dramatic improvement of symptoms. Cell replacement therapies have focused mainly on the use of human fetal mesencephalic tissue transplantation in patients with Parkinson's disease (PD).

WORLD FIRST TRANSPLANT THERAPY

In World first, a patient with Parkinson's disease has undergone transplant therapy, which uses reprogrammed stem cells to replace neurons destroyed by the disease.

Stem cell therapy is part of the toolkit

The stem cell field is an area of science that is relatively well funded and, out of all the branches of medical sciences relevant to aging, is probably the most understood by the public. In the last decade or so, progress in stem cell research has been rapid, and scientists now have wide range of cell types they can create on demand via cellular programming. While the majority of stem cell research is not specifically aimed at the defeat of age-related diseases, the technology could certainly be used to that end; hence, it is an essential part of the anti-aging toolkit. Stem cell exhaustion is thought to be one of the reasons we age, and, sooner or later, we will need to be able to replace losses; this research is an important step towards that goal.

Reprogramming cells

In general, most regular cells have specific functions in the body and in the tissues of which they are a part of. This specialization of cells into the myriad distinct types we see in the body allows our organs and tissues to do various things and is essential for us to live. While cells remain specialized once they develop into the desired cell type, it has been shown that they can change into other types of cells if they are given the proper chemical encouragement. In cellular reprogramming, researchers expose these specialized cells to certain chemicals that revert them back to an embryonic-like state from which they can then be guided to become other cell types. These flexible cells are known as induced pluripotent stem cells (iPSCs) and have been around for over ten years; however, this is the first time they have been trailed in a person with Parkinson's disease.

In October, the neurosurgeon Takayuki Kikuchi at Kyoto University Hospital performed the procedure, implanting 2.4 million of these precursor cells into 12 different areas in the brain of a 50-year-old patient.[13]

Replacing lost stem cells

Scientists used cellular reprogramming to turn iPSCs into the precursor cells of dopamine neurons, the cells whose loss is associated with Parkinson's disease. The destruction of these dopamine neurons is thought to lead to the classic tremors and walking problems that Parkinson's disease causes.

STEM CELL THERAPY: CHALLENGES AND PROMISES[14]

- Stem cell therapy and its uses for replacing damaged neurons in Parkinson's.
- "If successful, using stem cells as a source of transplantable dopamine-producing nerve cells could revolutionize care of the [Parkinson's] patient in the future," they say.
- "A single surgery," the authors go on to state, "could potentially provide a transplant that would last throughout a patient's lifespan, reducing or altogether avoiding the need for dopamine-based medications."
- More than 3 decades ago, pioneering studies that transplanted stem cells to treat Parkinson's used "fetal cells obtained from the midbrain of aborted embryos."
- However, there were numerous ethical issues with the procedure, as well as a host of side effects. These included transplant rejection and involuntary movements called dyskinesias.
- Recent advances in stem cell technology mean that the materials from which stem cells are derived are different and varied. For instance, researchers can use a person's own skin to collect pluripotent cells and reprogram them directly into neuronal cells.
- Cells can also be reprogrammed directly in the brain by injecting the conversion genes instead of the human skin cells. Researchers can also derive stem cells from the person's own blood.
- The first-generation cells are now being trailed and new advances in stem cell biology and genetic engineering promise even better cells and therapies in the future.
- It is very advanced technology in the treatment in the Parkinson's disease by replacing damaged neurons in Parkinson's

CONCLUSION

There is still no cure for PD since the precise mechanisms of this disease are largely unknown. High expectations have been placed on stem cell therapy to achieve this goal since many of the cell-based studies on PD animal models have shown positive results; however, the outcomes in clinical trials have not been consistent or convincing. This is possibly due to a combination of factors, such as patient selection, amount and mode of

tissue engraftment and the level of immuno suppression. Additionally, another side effect to be considered is GID. Fortunately, grafted tissues were not affected by PD progression within 10 years after transplantation, so the treatment of PD with stem cell grafts is still a promising direction. The major advantage of this strategy is the restorative and trophic abilities of the grafted cells which reach far beyond drugs prescribed in current practice.

Abbreviation

PD- Parkinson's disease
DA- Dopamine
OHDA- hydroxydopamine
VM- Ventromedial tissue
iPSC- induced pluripotent stem cell
ESCs- Embryonic Stem Cells
hESCs- human Embryonic Stem Cells
NSCs- Neural Stem Cells
MSCs- Mesenchymal stem cells
fNSCs- Fetal Brain Neural Stem Cells
CDNF- Cerebral Dopamine Neurotrophic Factor
NGF- Nerve Growth Factor
GDNF- Glial Derived Neurotrophic Factor
GID- Gender Identity Dysphoria

REFERENCES

1. Parkinson J. Essay on the shaking plasy. London: Sherwrood, Neely, and Jones, 1817.
2. Parkinson's disease Society. Parkinson's disease: the prsonal view. London: Parkinson's disease SocietyK, 1993.
3. Jorkliund A, Dunnett, Stenevi V, Lewis ME, Iversen SD. Reinnervation of the denervated striatum by substantia nigra transplant: functional consequences as revealed by pharmacological and sensorimotor testing. Brain Res, 1980; 199: 307-333.
4. Brownell AL, Livni E, Galpern W, Isacson O. *In vivo* PET imaging in rat of dopamine terminals reveals functional neural transplants. Ann Neurol, 1998; 43: 387-390.
5. Evans MJ, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. Nature, 1981; 292: 154-156.
6. Annett LE, Martel, Rogers DS. Behavioral assessment of the effects of embryonic nigral grafts in marmosets with unilateral 6-OHDA lesions of the nigro-striatal pathway. Exp Neurol, 1994; 125: 228-246.
7. Wood BH, Biclough JA, Walker RW. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. Journal of Neurology, Neurosurgery & Psychiatry, 2002; 72: 721-725.
8. Olanow CW, Goetz CG, Koldower JH. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol, 2003; 54: 403-414.
9. Dunnett SB, Hernandez TD, Summerfield A, Jones GH, Arbuthnot. Graft derived recovery from 6-OHDA lesions: specificity of ventral mesencephalic graft tissue. Exp Brain Res, 1998; 71: 411-424.
10. Hagell, Piccini, Bjorklund A. Dyskinesias following neutral transplantation in Parkinson;s disease. Nat Neurosci, 2002; 5: 627-628.
11. Dodel RC, Berger K, Oertel WH. Health related quality of life and healthcare utilization in patients with Parkinson's disease; impact of motor fluctuations and dyskinesias. Pharmacoeconomics, 2019; 19(10): 10130-1038.
12. Findley L, Aujla M, Bain PG. Direct economic impact of Parkinson's disease: A research survey in the United Kingdom. Movement Disorders, 2003; 18(10): 1139-1145.
13. Taba P, Asser T. Epidemilogy of Parkinson's disease. Reviews in Clinical Gerntology, 2004; 14(3): 211-28.
14. Freed CR, Breeze RE, Rosenberg NL. Neutral transplantation for the treatment of Parkinson's disease results at 1 year. Arch Neurol, 2003; 2: 437-445.