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Systematic Review

A new area of stem cell therapy for Parkinson disease

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ABSTRACT

No treatment currently can be used in order to slow or even stop the progression of Parkinson's disease. Nowadays, researchers are already using stem cells to grow dopamine-producing nerve cells in the lab so that they can study the disease, especially in those cases where there is a known genetic cause for the condition. The development of the advanced cellular therapies and using induced pluripotent stem cells is making it possible to combat the progression of the disease without the resulting motor complications. It has been shown that the transplantation of many cell sources leads to reduce Parkinson's disease symptoms in animal models.

Keywords: Parkinson's disease, Stem cells, Pluripotent stem cells, Alpha synuclein, Animal model, Cell therapy, Dopaminergic neurons, Induced pluripotent stem cells, Neurodegeneration

INTRODUCTION

Parkinson's disease (PD) is a brain disorder that leads to shaking, stiffness, and difficulty with walking, balance, and coordination. In other words, PD is a progressive nervous system disorder that affects movement.[1] It has been shown that people with PD don't have enough dopamine. Dopamine is a chemical that allows messages to be sent to the parts of the brain that in order to control the processes of movement and thinking. In PD patients, the disease targets and kills dopamine producing nerve cells, or neurons, in part of the brain called the substantia nigra, although the disease does affect other nerve cells inside the brain which may cause some of the other characteristics of Parkinson's such as problems with thinking, motivation, sleep, etc. Parkinson's is also lead to the formation of accumulation of a protein called alpha-synuclein in the brain. These abnormal protein clumps are called Lewy bodies. As dopamine nerve cells die, tremors are developed in Parkinson's patients, and their developments slow down. They might also suffer

from sleep disorders or lose their sense of smell, depression, constipation and sometimes dementia in last stages of the disease as the disease spreads out to involve other nerve.[2]

Stem cells

A stem cell is a cell with the unique ability to develop into specialized cell types in the body. Researchers have found that in the future they may be used to replace cells and tissues that have been damaged or lost due to disease. Stem cells are an unlimited source of the differentiated cells that make up the tissues and organs of animals and plants. There is great interest in stem cells because they have potential in the development of therapies for replacing defective or damaged cells resulting from a variety of disorders and injuries, such as Parkinson disease, heart disease, and diabetes. There are two major types of stem cells: embryonic stem cells and adult stem cells, which are also called tissue stem cells.[3]

Here in this study, the researchers discuss the implications of stem cell therapy for Parkinson's disease using induced pluripotent stem cells Parkinson's disease models in vitro.

Stem cell types

Embryonic stem cells (ESCs) Stem cells that come from a human embryo, basically at early developmental stage. In this type of stem cells, embryos formed by in vitro fertilization (IVF). (This is as against to fetal stem cells that are derived from an older embryo.)

Adult derived stem cells (also called tissue-specific stem cells): Stem cells that can be found among differentiated cells and then can be isolated from these adult cells. The most well-known of these cells are hematopoietic stem cells thoses can be found in adult blood and bone marrow, which have been used clinically for decades, typically to treat blood cancers and other disorders of the blood and immune systems.

Umbilical cord stem cells: Hematopoietic stem cells are also found in umbilical cord blood that is restored after delivery. These stem cells are used medically to treat blood cancers and some uncommon genetic disorders.

Mesenchymal stem cells also known as stromal cells are existent in many tissues inside vital bodies such as fat, cartilage and bone. They still understood, however likely the ability to renewal potential. These are the cells that are commonly collected at the commercial stem cell clinics that are described above.

Induced pluripotent stem cells (iPSCs): Stem cells generated from adult skin or blood cells that have been reprogrammed to return to an embryonic state.

Human parthenogenetic stem cells: Stem cells created from an unfertilized human ovum.

Induced pluripotent stem cells Parkinson's disease models in vitro

It is clear that when trying to model and study PD is to study the unique qualities of induced pluripotent stem cells (iPSCs) provide many advantages. Fibroblasts are large, flat-like structure. Also, fibroblasts are elongated (spindle-shaped) cells possessing processes extending out from the ends of the body of the cell. Fibroblasts can be taken from an individual suffering from PD, reprogrammed to a pluripotent state using transcriptional factors, and then differentiated into the midbrain Dans directly affected by PD. In fact, animal models are a great candidate for testing cell therapies' efficacy. Model organisms (Drosophila, yeast, mice, and non-human primates) have also contributed significantly to our understanding of PD.[4]

METHODS

It has been shown that the disorder in synuclein-alpha, encoding α-synuclein, was the first gene linked to familial PD. Moreover, multiple genome-wide association researches have showed that changes at the SNCA locus is the most significant genetic risk factor for sporadic PD. So, a potential solution is to use a special technology such as reprogamming technology to generate disease-specific induced pluripotent stem cells (iPSCs). Directed differen tiation to dopaminergic neurons. In this study we used a special culture called a feeder-free monolayer culture method in order to induce neural differentiation under defined conditions, via dual inhibition of SMAD signalling. This approach contains noggin (an inhibitor of BMP4) and SB431542 (an inhibitor of lefty/activin/TGFβ pathways) to achieve robust neural differentiation. To improve efficiency and to reduce costs, we have added dorsomorphin (a chemical BMP inhibitor) as a partial substitute for noggin. Also, a special protocol called SMAD has been employed to generate floor plate tissue from human embryonic stem cells (ESCs). Moreover, the researchers demonstrated directed differentiation of human ESCs into floor plate tissue via initial dual SMAD inhibition in conjunction with early high-dose sonic hedgehog (SHH) signaling. The researchers commenced neural differentiation with dual SMAD inhibition for 1 day, followed by SHH, WNT1 and Dkk1 blocking antibody treatment. After 9 days of floor plate differentiation, the protocol was switched to promote maturation of midbrain dopaminergic neurons from neural progenitors derived from human ESCs.[5-7]

Eight AST and six NAS iPSC lines were subjected to the floor plate-dopaminergic differentiation protocol. In order to analyze the results, five aspartate transaminase (AST) lines and four NAS lines produced viable neurons that could be analyzed. After 20 to 31 days, differentiated iPSCs were examined for tyrosine hydroxylase (TH - the

rate-limiting enzyme in the biosynthetic pathway to dopamine, used as a marker of dopaminergic neuronal identity) and neuron-specific class III β-tubulin (TuJ1 - used as a marker of pan-neuronal identity) and all showed robust expression of these markers. We performed blind cell counts on micrographs fluorescently labelled for TH and TuJ1, and found that AST iPSCs yielded 37% (SD 5) TH-positive cells as a proportion of TuJ1-positive cells whereas NAS iPSCs yielded 28% (SD 4), which is not significantly different. Hence, we assured that the midbrain identity of these TH-positive neurons by co-immuno labelling with the ventral midbrain marker LMX1B. To further confirm their midbrain dopaminergic identity, an expression analysis we performed of LMX1A, NURR1, TH and DAT. We observed a range of expression of these factors that was not linked to genotype. This may reflect clonal variation or efficiency of neutralization that has been previously observed in iPSCs. Obviously, genome-wide single nucleotide polymorphisms (SNP) analysis of AST iPSC-derived neuronal cultures suggested that the triplication region had remained intact during differentiation.[8,9]

RESULTS

Repairing the brain

Basically, researchers are aiming to explore how to replace the neurons that are destroyed in nervous system disorders that are caused when neurons are gummed up by abnormally folded and clumped up proteins such as Parkinson's disease. They have been developing new methods to restore nervous system function by turning one type of already differentiated motor neuron into another. Obviously, this type of studies has broad implications especially for Parkinson's. Researchers in this filed want to know how these reprogrammed cells do their functions in the brain and use this understanding to rebuild brain cell connections destroyed by amyotrophic lateral sclerosis (ALS) and Parkinson's. The highly advances in stem cell technologies ease the route to take a small piece of skin from a patient and turn the skin cells into stem cells (hence-called "induced pluripotent stem cells" or iPS cells). That is to said, can make any tissue in the body, including brain cells. Also, it is possible now to see the abnormalities that result from protein misfolding in stem cell-derived neurons from Parkinson's disease patients.

This study is among the studies that are focusing on how to repair brain regions affected by diseases like Parkinson's.

This type of studies together are complementary approaches that will rise our understanding of what causes Parkinson's disease, how it occurs and progresses, and how damaged neurons can be repaired. The collaborations will accelerate the translation of basic Parkinson's research into clinical treatments for the disease.

DISCUSSION

It has been shown that iPSC technology has the ability to give us better understanding of PD, because it provides the opportunity to generate and study disease-affected cells cell models directly from patients. iPSC technology has already been used to generate for neurological cell models such as: amyotrophic lateral sclerosis, sporadic PD, spinal muscular atrophy and familial dysautonomia have all been described. In this study, we describe iPSC lines, more specifically, triplication of SNCA (AST), and lines from a non-affected first-degree relative (NAS). Each sets of iPSC lines were monitored for retroviral transgene silencing, pluripotent marker expression, and differentiation efficiency in a floor plate-dopaminergic neuronal specification protocol. All of the lines derived from the PD patient fibroblasts have the SNCA triplication intact, as determined by PCR on genomic DNA, and confirmed in a subset of lines with genome-wide SNP analysis. It has been found that the subsets of iPSC lines from the patient and unaffected relative successfully differentiated into dopaminergic neurons.10 These lines passed all criteria, and patient-derived neurons exhibited a doubling of SNCA mRNA expression and α-synuclein protein. We assigned a number of potential variables that must be considered when establishing an iPSC disease model. Differences between iPSC clones, differences in their responses to variant differentiation protocols, and heterogeneity of neural differentiation all should be accounted when we consider the availability and robustness of pluripotent cell lines that are used to model many human diseases such as PD. These sources of changes have also been seen in other iPSC models.[11] That is to said, generating several independent iPSC lines from each patient involved in a study of this nature is a must and this is to examine the efficiency of neutralization for fair comparisons to be made. According to our study and as what we expected, each differentiated patient-derived iPSC clone to give a doubling of SNCA expression despite that we used a simple and robust system for examining the activity of the iPSC disease-modelling field. To modelling diseases such as PD using the application of iPSC technology considering both the long latency and involvement of epigenetic factors that could be erased during reprogramming is challenging. For this reason, we aimed to choose an early onset, rapidly progressive, fully penetrant familial PD to offset these two potential problems as far as possible. We added many extrinsic factors in order to stimulate oxidative stress. In many preceded studies, this has recently been conducted to investigate LRRK2 mutant iPSCs24. PD iPSC models are systems that give us the ability to study the earliest pathogenic changes that lead to, rather than ones in which end-stage pathology of PD is observed.[12] Due to the fully penetrant and early-onset phenotype in humans, the triplicated SNCA iPSCs are well positioned for these studies. We did that because determining these earliest responses might provide a method by which the disease can be stopped before it progresses. Also, we studied the

pathological changes that occur during the disease in order to know if they are protective rather than toxic. We also carry iPSCs triplication to provide a valuable tool to study deeply cell-to-cell propagation of pathology, being primed to develop disease. These cells will also be of value in studying other synucleinopathies in vitro.[13] Based on clinical views, SNCA triplication can generate the full understanding of the synucleinopathies, including progressive supranuclear palsy, multiple system atrophy and dementia with Lewy bodies, as well as PD. According to Pathology, cases can contain glial deposition of α-synuclein reminiscent of the glial cytoplasmic inclusions found in multiple system atrophy. The differentiation of AST and NAS lines towards an oligodendroglial fate may be to inform about the cellular techniques operating in this disorder.[14,15]

CONCLUSION

Nowadays, researchers are able to produce multiple induced pluripotent stem cell lines from an SNCA triplication PD patients. In light of the above-mentioned results, it has been shown that the patient produces double the amount of α-synuclein protein as neurons from the unaffected relative, precisely recapitulating the cause of Parkinson's disease in these individuals when these cells are differentiated into midbrain dopaminergic neurons. This is a new experimental design that helps to identify compounds which decrease levels of α-synuclein, and to study deeply the mechanistic basis of neurodegeneration caused by α-synuclein dysfunction.

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