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The promises of stem cells: stem cell therapy for movement disorders

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SUMMARY

Despite the multitude of intensive research, the exact pathophysiological mechanisms underlying movement disorders including Parkinson's disease, multiple system atrophy and Huntington's disease remain more or less elusive. Treatments to halt these disease progressions are currently unavailable. With the recent induced pluripotent stem cells breakthrough and accomplishment, stem cell research, as the vast majority of scientists agree, holds great promise for relieving and treating debilitating movement disorders. As stem cells are the precursors of all cells in the human body, an understanding of the molecular mechanisms that govern how they develop and work would provide us many fundamental insights into human biology of health and disease. Moreover, stem-cell-derived neurons may be a renewable source of replacement cells for damaged neurons in movement disorders. While stem cells show potential for regenerative medicine, their use as tools for research and drug testing is thought to have more immediate impact. The use of stem-cell-based drug screening technology could be a big boost in drug discovery for these movement disorders. Particular attention should also be given to the involvement of neural stem cells in adult neurogenesis so as to encourage its development as a therapeutic option.

1. Introduction

Scientists have known of the existence of stem cells, the unspecialized cells found in all multicellular organisms that can self-renew through self-division and differentiate into diverse specialized cell types, for over a century. Yet it has been only since the late 1990s, when human embryonic stem cells were first cultured in the laboratory, that the field of stem cell research has become the focus of intense scientific interest.

There are essentially three kinds of stem cells: embryonic stem (ES) cells, which are isolated from the inner cell mass of blastocysts; adult stem cells, which are found in various developed tissues such as bone marrow cells; and induced pluripotent stem (iPS) cells, which are artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing a "forced" expression of specific genes.

One of the most astounding applications of stem cells is in the treatment and cure of a wide variety of movement disorders including Parkinson's disease (PD), multiple system atrophy (MSA) and Huntington's disease (HD). Several ways of how stem cells are being explored and used in both basic and clinical applications of current movement disorders research include disease modeling, drug toxicity screening/drug discovery, gene therapy and cell replacement therapy.

In most cases, it is difficult to obtain the damaged cells in a disease and to study them in detail. Stem cells, either carrying the disease gene or engineered to carry disease genes, offer an alternative for laboratory studies. Researchers are able to model disease processes *in vitro* and perform more relevant and informative biological assays, thereby better understanding the mechanisms underlying the disease. Stem cells have also been used in the laboratory to screen for new drugs. It has been revealed that very few drugs have been tested on human-diseased cells before human testing. Liver and heart toxicity problems account for about 30% of drugs that fail in early-stage clinical trials, indicating a need for more efficient means of drug toxicity testing before clinical trials. The use of stem cells with specific diseases may correct this situation. Furthermore, given their unique regenerative abilities, stem cells offer the possibility of a renewable source of cell replacement therapies for neurological diseases.

However, stem cell research has been controversial and has raised ethical dilemmas primarily concerning the creation, treatment, and destruction of human embryos inherent to research involving ES cells. The recent discovery of iPS cells, hailed as a potential alternative to ES cells, provides researchers with a unique tool to derive neurons from patient-specific iPS cells for the study of neurological diseases. More importantly, iPS cell research obviates many ethical and resource-related concerns posed by ES cells while prospectively matching their potential for scientific use.

In recent years, the discovery of constitutive ongoing neurogenesis in the adult human brain has challenged the traditional view of a fixed circuitry in functionally normal brains, and has raised high hopes that the adult brain may have the capacity for self-renewal

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after injury, thereby sidestepping the need for transplantation. Primary neural precursor cells reside in specialized zones called "neurogenic niches". A population of neural stem cells (NSCs) preserves enough germinal character to maintain neurogenesis throughout life and, once differentiated, their daughter cells integrate into already existing neuronal networks. Whether adult neurogenesis can be induced under certain circumstances in regions that lack constitutive adult neurogenesis remains controversial, but several studies have reported the isolation of NSCs from different regions of the adult brain, including the substantia nigra pars compacta (SNc). Therefore, there has been considerable interest within the scientific community to gain understanding of the possible correlation between neurogenesis and pathogenesis of movement disorders, which could help the future development of novel therapeutic intervention.

2. Stem cell therapy for PD and MSA

There has been a long history of fetal tissue transplantation for the treatment of patients with advanced PD. Despite the wake of a long series of encouraging open-label studies, initial enthusiasm for cell replacement therapy by grafting fetal neuronal precursor cells into the striatum has vanished after two double-blind placebo-controlled clinical trials showing only moderate symptomatic improvement and the occurrence of severe disabling dyskinesia. These problems should be solved before fetal tissue transplantation can be considered a therapeutic option for PD [1].

Studies have shown ES cell transplanted into the brains of PD rat model differentiated into dopaminergic neurons, restoring partial neural function [2]. PD rodent models subjected to engraftment of dopaminergic neurons derived from human ES cells demonstrated complete behavioral restoration and motor function improvement. Similarly, parkinsonian monkeys receiving transplantation showed excellent DA neuron survival, function and lack of neural overgrowth, indicating potential for the development of cell-based therapies in PD [3].

It was recently shown that reprogramming mouse embryonic fibroblasts with four transcription factors Oct4, Sox2, Klf4, and c-Myc induces pluripotency [4], enabling generation of iPS cells from patients with a variety of diseases [5]. iPSC-derived midbrain dopaminergic neurons from a patient with a triplication in the α-synuclein gene (SNCA) showed accumulation of α-synuclein, inherent overexpression of markers of oxidative stress, and sensitivity to peroxide-induced oxidative stress, precisely recapitulating the cause of disease in the patients [6,7]. Comparably, PARK2 iPSC-derived neurons exhibited mitochondrial dysfunction associated with increased oxidative stress and α-synuclein accumulation, resembling pathogenic changes in patient brains [8]. Neurons derived from mutant PINK1 iPS cells displayed impaired recruitment of lentivirally expressed Parkin to mitochondria, increased mitochondrial copy number and upregulation of PGC-1α, an important regulator of mitochondrial biogenesis, upon mitochondrial depolarization [9]. LRRK2 mutant iPSC-derived DA neurons demonstrated increased susceptibility to oxidative stress, consistent with existing understanding of early PD phenotypes [10]. Such disease-specific iPS cells offer an unprecedented opportunity to recapitulate both normal and pathologic human tissue formation *in vitro*, thereby facilitating disease investigation and drug development.

Furthermore, generation of iPS cells provides a new avenue for transplantation therapy as it can avoid immunorejection, a major complication in current transplantation medicine. Wernig et al. [11] reported upon transplantation into the fetal mouse brain, iPSC-derived neural precursor cells extensively differentiate into glia and neurons. Functional recovery was observed after transplantation of iPSC-derived midbrain dopamine neurons into the adult brain of Parkinsonian rats. Risk of tumor formation from grafted cells was minimized by the separation of contaminating pluripotent cells and committed neural cells using fluorescence-activated cell sorting. Encouraging data from rodent studies then prompted subsequent assessment in a primate model. Kikuchi et al. [12] observed that human iPSC-derived neural progenitor cells grafted in the brain of a primate PD model survived as dopaminergic neurons for as long as six months, implying the therapeutic potential of human iPS cells. Direct reprogramming of mouse and human fibroblasts into induced neural stem cells (iNSCs) has been proven feasible with a single factor, Sox2. iNSCs express NSC markers and resemble wild-type NSCs in their morphology, self-renewal, ability to form neurospheres and differentiate into several types of mature neurons as well as astrocytes and oligodendrocytes, indicating multipotency. Importantly, implanted iNSCs can survive and integrate in mouse brains without tumorigenic potential. As an additional merit, this method allows shortening of the duration for neuronal cell creation from fibroblasts [13].

Adult stem cells comprise mesenchymal stem cells, hematopoietic stem cells, ectodermal stem cells and so on. Scientific interest in adult stem cells is spotlighted on their ability to divide or self-renew indefinitely, and generate all the cell types of the organ from which they originate, potentially regenerating the entire organ from a few cells. Numerous studies using expanded and/or induced bone marrow-derived mesenchymal stem cells have been reported for animal models and yet only three clinical studies with intracerebral or intravasal application of these cells have been reported for PD and MSA patients. In two open-label studies, subventricular application of both allogenic and autologous bone marrow-derived mesenchymal stem cells showed improvement of motor behavior as reflected by reduction of UPDRS ON and OFF scores in most but not all PD patients [14,15]. In a randomized placebo-controlled trial involving a small number of cognitively intact MSA-C patients, mesenchymal stem cell therapy was safe and was able to delay the progression of neurological deficits with functional improvement in the follow-up period in some of the patients [16].

3. Adult neurogenesis in Parkinson's disease

Increasing evidence points to the presence of adult neural stem cells in many areas of the mammalian brain, mainly in the hippocampus and subventricular zone (SVZ) near the lateral ventricle. It is well known that changes occurring in the SVZ depend upon the pathological condition. Dopamine is an important molecule in neurogenesis. Therefore many investigators now focus on neurogenesis in PD. Höglinger et al. [17] reported reduction in the numbers of proliferating cells in the SVZ of postmortem brains of PD patients, implying that generation of neural precursor cells is impaired in PD as a consequence of dopaminergic denervation. However, controversy regarding neurogenesis in the SVZ in PD models persists. Some groups reported decreased neural precursor proliferation while some reported increased neural precursor proliferation in the SVZ of PD models.

Likewise, whether dopaminergic neurogenesis occurs in the adult substantia nigra (SN) in PD brains or in PD animal models remains a matter of debate. So we evaluated nigral neurogenesis in animal models and PD autopsy brains. We first performed retroviral labeling in a PD rodent model and observed efficient labeling of proliferating cells in SN with retroviral transduction of green fluorescent protein. But many of these labeled cells became microglia and none had differentiated into tyrosine-hydroxylase (TH)-positive neurons. Second, staining for intrinsic markers of neurogenesis showed that there were no proliferating cells in the SN of PD patients but a large number of polysialylated neural cell