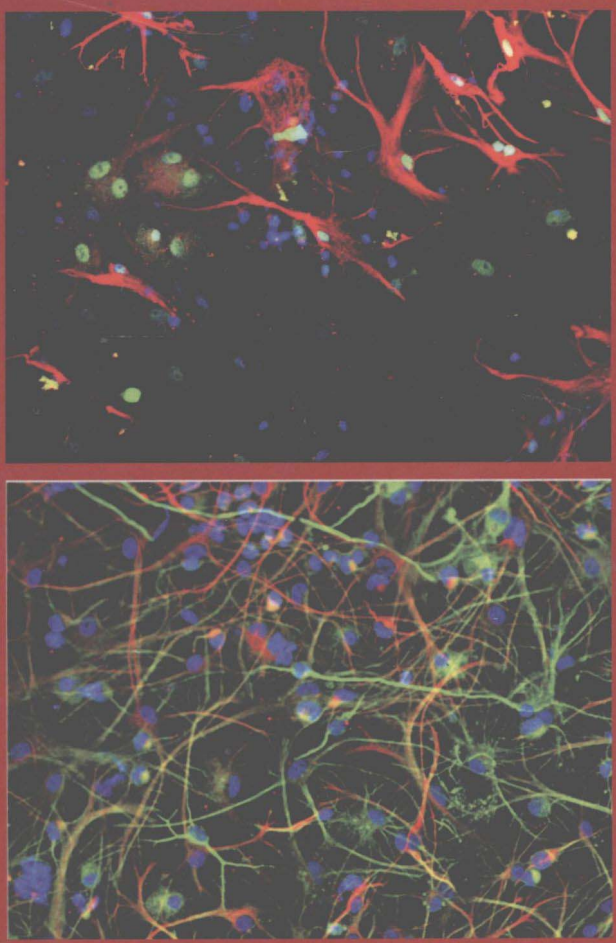
Stem Cells and Neurodegenerative Diseases



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Stem Cells and Neurodegenerative Diseases

Dedication

Christopher Reeve once said:

> *"So many of our dreams at first seem impossible, then they seem improbable, and then, when we summon the will, they soon become inevitable."*

It is the belief of the three editors of this book that during the first half of this new century we will see the clinical use of stem cells to treat a host of neurological and neurodegenerative disorders. This book is dedicated to the patients and their family, friends, and caretakers, as well as those who dedicate their lives to finding cures for the devastating disorders of the nervous system.

Preface

In the last decade, research on embryonic and adult stem cells has greatly expanded as the interest in their use in regenerative medicine continues to grow. Pluripotent stem cells can give rise to over 200 different cell types and therefore present a great opportunity for new therapeutic approaches. In addition, the use of adult stem cells and reprogrammed somatic cells (such as inducible pluripotent stem cells; iPSCs) may provide patient-specific treatments, while circumventing the ethical concerns surrounding the use of embryonic stem cells.

Results from numerous experimental studies as well as growing evidence from early clinical research indicate that stem cell therapy has significant potential for improving the quality of life for patients with a variety of neurological disorders, including spinal cord injury, stroke, multiple sclerosis, and neurodegenerative diseases (such as Parkinson's and Huntington's diseases). Pre-clinical investigations and some of the new clinical studies suggest that stem cell transplantationcan reduce cell death and promote neuroprotection after spinal cord injury or stroke by providing trophic support and, as suggested from the results of some trials, by replacing lost cells and remyelinatingaxons in the damaged brain. At the very least, it appears that stem celltransplantscan create a favorable environment in the brain that is capable of promoting neuroplasticity, neuronal regeneration, or a supportive milieu that translates into reductions in neuropathology and amelioration of functional deficits. In order to develop a better understanding of how transplantation of stem cells orchestrate their beneficial effects so that their use can be optimized, it is important to study both their intrinsic qualities as well as their interactions within the host environment. Indeed, insights into the importance of specialized stem cell niches that allow for the ideal amount of plasticity can help in determining the optimal number of cells to transplant, as well as critical factors affecting fate decision, migration and differentiation. Determining what the ideal balance between stem cells and their progenitors should be within specific transplant areas is critical for ensuring that the damaged brain receives the correct type and number of neuronal and glial cells for reducing cell death, replacing lost neurons, or correcting demyelinating

conditions, such as in multiple sclerosis. This balance is also critical in future efforts for treating disorders, such as Alzheimer's disease, in which adult neurogenesis is altered through direct and indirect mechanisms, causing a microenvironmental imbalance within the brain, including the sub-ventricular stem cell niche.

In addition, there is strong evidence from animal studies that supports the use of stem cell therapies in cases of vascular network disruption (such as ischemic stroke). However, as is the case with observed benefits in many neuronal disorders, the mechanisms whereby stem cell transplants exert their ameliorative effects are not fully understood. Clearly, additional research is needed before the pervasive use of stem cell transplant strategies is undertaken to treat many of the disorders or for the repair of damaged brain tissue in humans can be safely pursued.

With regards to multipotent stem cells, it is now well documented that neural, and especially mesenchymal stem cells (when transplanted into the brain) display immunosuppressive properties which are particularly advantageous for treating the damaged brain, given that almost all types of brain damage, including traumatic brain injury, stroke, and even most neurodegenerative disorders, are accompanied by significant inflammation. Thus, controlling the intensity of this immune response is one of the critical keys to reinstate some of the lost function following brain damage. Research into how some stem cells avoid immunosurveillance mayprovide new insights into how one might maximizetherapeutic their therapeutic potential, perhaps even to the extent of expanding applications in transplantation of xenogeneic neurons for treating brain damage.

Another research direction of intense interest is the role that both endogenous and transplanted stem cells may be playing in formation of brain tumors. In order to better understand how neural stem cells interact with brain cancers, such as gliomas, new studies on brain tumor development are being conducted. Recent work in this area suggests that the cancer stem cell phenotype is interrelated with, and participates in, tumor recurrence and drug resistance. Therefore, a better understanding of how both normal stem cells and cancer stem cells function and interact is required before stem cell therapy can be used to safely treat brain tumors in humans.

Recently, the generation of iPSCs has opened a new frontier in stem cell therapy by allowing the creation of cell models for genetic disordersof the nervous system that provides an enormously useful to explore the mechanisms underlying such diseases. The iPSCs have the potential to allow for targeted autologous cell transplantation that is not only patient-specific, but may provide for more extensive differentiation into the type of neurons or glial cells that are needed than what may be possible with MSCs for exemple. Although most of the initial work with iPSCs are as screens for

potential pharmacological treatments of various diseases, primarily because of initial concerns that they readily produce tumors when transplanted into the brain, more recent work suggests that these cells have enormous potential for possible cell replacement therapies.

In conclusion, stem cell therapies offer significant hope for the millions of people around the world who are suffering from some type of neurological disorder. Estimates are that disease and damage to the nervous system will soon affect about one-third of the world's population. To address this growing need, more efficient interactions between researchers and clinicians, as well as between scientists, healthcare providers, and policymakers must be achieved. In addition, better communication between scientists, healthcare providers, and policymakers and the general public will be needed if regenerative medicine using stem cell transplantation is to become a viable treatment for the growing number of patients suffering from brain damage or neurodegenerative disorders.

The editors and authors of this book have invested a great deal of their time to move stem cell therapies forward. We firmly believe that stem cell therapies have significant potential to help those who need it most. We hope that the information provided in this book will be of use for fellow scientists, policymakers, and those in the general public who want to learn more about the exciting new developments in stem cell therapies.

Laurent Lescaudron, Ph.D
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Contents

1

Stem Cells as a Source for Cell Therapy in Parkinson's Disease

J. Ganz, N. Lev and *D. Offen**

Introduction

Parkinson's disease (PD), the second most common age-related progressive neurodegenerative disorder, is characterized by the loss of dopaminergic (DA) neurons, intracellular inclusions of aggregated proteins and neuroinflammation (Bjorklund, 2005). The most prominent symptoms of PD are tremor, rigidity, bradykinesia, and postural instability (Arenas, 2010). As symptoms progresses, patients will develop difficulties in walking, talking, or completing simple tasks. Moreover, later symptoms could include psychiatric, autonomic and cognitive disorders (Beck, 1995; Weisman and McKeith, 2007). The pathologic hallmark of PD is primarily the progressive degeneration of dopaminergic neurons in the *substantia nigra pars compacta* of the ventral midbrain, resulting in a dopamine deficiency in the nigrostriatal pathway (Arias-Carrion et al., 2007). Currently there is no cure or effective treatment for PD and numerous approaches to slow the neuronal loss or stop the disease progression have failed (Yokochi, 2009). Dopamine agonists, levodopa, enzyme inhibitors, and deep brain stimulation are being routinely used for treating PD patients, but their efficacy is very limited (Lindvall and Kokaia, 2010).

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As a novel and alternative approach, cell replacement therapy (CRT) emerged three decades ago for treating PD patients. Due to the selective loss of a specific subset of a neuronal population, it was challenging to study the possible effect of direct replacement of new and healthy A9 DA neurons. Several clinical studies demonstrated that replacement of lost dopaminergic (DA) neurons could improve motor symptoms of PD patients (Freed et al., 1992; Hoffer et al., 1992; Lindvall et al., 1989). Since the concept of CRT emerged, many obstacles restricted its use (Ganz et al., 2011). The complexity of the experimental design still depends on which cells are the safest and best suited to provide functional A9 DA neurons and where to transplant them in order to functionally reestablish the DA system.

The Path of Cell Therapy for Parkinson's Disease

Seminal works from Björklund and Stenevi (Björklund et al., 1976; Stenevi and Björklund, 1978; Stenevi et al., 1976) and Olson, Seiger and Hoffer (Freed, 1980; Hoffer, 1975; Olson, 1972; Seiger, 1976) represents the initiation of the concept of cell therapy for PD. Given the loss of DA neurons in the caudate and putamen at the striatal level, it was conceived that by providing new dopamine from dopamine secreting cells transplants, the activity of the affected areas depleted from DA neurons could be restored. It was shown that striatal grafts of ventral mesencephalon (VM)-derived fetal dopaminergic cells, improved motor functions of PD patients. However, nigral grafts failed to improve motor functions, due to axon extension failure and lack of nigro-striatal reestablishment (Björklund et al., 1983a; Björklund et al., 1983b; Brundin et al., 1986a; Brundin et al., 1986b; Brundin et al., 1987; Dunnett et al., 1983a; Dunnett et al., 1983b; Wakeman et al., 2011). Adrenal medullary grafts also showed positive results in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated monkeys and rats (Freed et al., 1981; Morihisa et al., 1984). The first clinical trial using adrenal cells reported positive results, but further trials demonstrated less favorable outcomes (Goetz et al., 1989; Madrazo et al., 1987). Since those years, hundreds of patients, receiving various grafts, have been evaluated, showing a 30–60% improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) in most of the patients with a positive clinical outcome during the off-drug period (Vidaltamayo et al., 2010). Histological examination found that grafted cells survived at least 10 years after transplantation (Freed et al., 2001). Moreover, they showed that grafts effectively reinnervated the affected striatum and restored striatal dopamine release. However, double-blind, placebo-controlled studies, using embryonic mesencephalic tissue, failed to significantly improve the outcome of PD. Currently, and due to stem cells research, many alternative approaches have been developed to generate DA neurons. Cells that function like dopaminergic neurons,

have dopaminergic phenotypes, and confer similar therapeutic effect can now be obtained from different cellular sources (Cai et al., 2010; Kim et al., 2002; Levy et al., 2008; Murrell et al., 2008; Park et al., 2008a; Yasuhara and Date, 2007).

One cell source that provides many of the qualities of transplanted dopaminergic cells is bone-marrow-derived mesenchymal stem cells (BM-MSCs). However, is still under debate if these cells can trans-differentiate into the ectodermal lineage and generate functional neurons. Recently, a clinical study was performed in India assessing the potential of unilateral autologous BM-MSC transplantation in PD patients (Venkataramana et al., 2010). Even though the clinical improvement was marginal, this study established the safety of autologous BM-MSCs transplantation. Another published study evaluated treatment of PD with intra-arterial autologous implantation of adult stem cells (Balasubramanian et al., 2009). It reported that intra-arterial implantation of stem cells is feasible and safe and results in a decrease in the severity of the disease and an increase in the quality of life for patients receiving the treatment. Currently, several clinical studies involving stem cells for treating PD are being performed, according to the US National Institute of Health (www.clinicaltrials.gov). These trials are mostly based on autologous transplantation of BM-MSC in PD patients, with the main goal of determining procedure safety and efficacy (clinical trials references NCT00976430, NCT01446614, NCT01453803). Furthermore, three more studies are focusing on stem cell sampling and development of therapeutic procedures, generating human iPS cells from skin biopsies or patient's hair (NCT00874783), mesenchymal stem cells as replacement tissue for PD (NCT00033774) or development and optimization methods to isolate, propagate and differentiate adult human neural stem cells from patients with PD (NCT01329926).

Clinical Experiences

One of the major questions about CRT in PD is why all the encouraging result obtained in animal models have failed to be translated in the human clinical trials? There are several possible explanations. First, experimental models always recapitulate the disease only partially. The animal models used to model PD are generally acute injuries, employing the injection of neurotoxic agents. PD pathology in humans is not acute, but a progressive chronic degenerative process that last several decades. Second, the environment to which the transplanted cells are exposed in animal models differs considerably from diseased human brains. Neurodegenerative diseases, such as PD, present highly deranged environment which includes among others, heavy oxidative stress, protein aggregation and trophic support deficiencies induced by malfunction of neuron-support cells.

These abnormalities are less prominent, or even non-existent, in animal models. Third, most transplant patients have suffered from long-lasting and severe forms of the disease, so a selection of better suited, perhaps less chronically afflicted, patients could lead to more positive outcomes following transplantation. These differences are not trivial and might be of major importance when trying to translate a therapy developed in homogenous animal models to humans. Expectations should be limited, and defining the best-suited patients for the therapeutic intervention is imperative.

During the clinical trials performed over the years, the development of significant graft-induced dyskinesias (GIDs) has been reported. GIDs are involuntary movements that occur in the absence of medication, but in the presence of the graft. Freed and colleagues (2001) reported GIDs in 15% of the transplanted patients more than 1 year post-transplant. Several of these patients required further surgical intervention with subthalamic deep brain stimulation (DBS) to help alleviate these troublesome GIDs (Olanow et al., 2001). A placebo-controlled study by Olanow and colleagues (2003) also reported the development of significant "off-medication" GIDs in 56.5% of the grafted patients at 6–12 months after transplantation (Olanow et al., 2003). These GIDs typically consisted of stereotypic, rhythmic movements of one or both lower extremities, with three of the patients requiring further surgical intervention to reduce their severity. Importantly, GIDs were described only in patients who suffered previously from L-DOPA-induced dyskinesias, yet without correlation to their severity (Brundin et al., 2010).

The first theory of the origin of GID was that it stemmed from imbalanced dopaminergic innervation. It has been suggested that GIDs developed as a result of fiber outgrowth from the graft, causing increased DA release (Freed et al., 2001) or as a result of imbalanced DA reinnervation (Ma et al., 2002; Politis, 2010). Immunological implications have also been proposed in which inflammatory responses are triggered against the graft (Olanow et al., 2003). This goes in line with the clinical observation of GIDs occurred after early discontinuation of immunosuppressive therapy with signs of inflammatory reactions around the graft, as seen in autopsied subjects (Olanow et al., 2003; Piccini et al., 2005). Another theory is that GIDs are a consequence of contamination of serotonergic (5-HT) neurons that were co-grafted in these tranplants. Since 5-HT neurons are physiologically able to store and release DA, GIDs can occur as a result of DA levels mishandling. This latter hypothesis proposes that 5-HT neurons are responsible for dysregulation of the DA release in the synapse as a result of graft-derived excess of 5-HT neurons interacting with the normal DA neurons (Politis et al., 2010).

Using *in vivo* brain imaging, Politis and colleagues (2011) observed excessive serotonergic innervation in the grafted striatum of two patients