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Review

Advantages of nonhuman primates as preclinical models for evaluating stem cell-based therapies for Parkinson's disease

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ABSTRACT

The derivation of dopaminergic neurons from induced pluripotent stem cells brings new hope for a patient-specific, stem cell-based replacement therapy to treat Parkinson's disease (PD) and related neurodegenerative diseases; and this novel cell-based approach has already proven effective in animal models. However, there are several aspects of this procedure that have yet to be optimized to the extent required for translation to an optimal cell-based transplantation protocol in humans. These challenges include pinpointing the optimal graft location, appropriately scaling up the graft volume, and minimizing the risk of chronic immune rejection, among others. To advance this procedure to the clinic, it is imperative that a model that accurately and fully recapitulates characteristics most pertinent to a cell-based transplantation to the human brain is used to optimize key technical aspects of the procedure. Nonhuman primates mimic humans in multiple ways including similarities in genomics, neuroanatomy, neurophysiology, immunogenetics, and age-related changes in immune function. These characteristics are critical to the establishment of a relevant model in which to conduct preclinical studies to optimize the efficacy and safety of cell-based therapeutic approaches to the treatment of PD. Here we review previous studies in rodent models, and emphasize additional advantages afforded by nonhuman primate models in general, and the baboon model in particular, for preclinical optimization of cell-based therapeutic approaches to the treatment of PD and other neurodegenerative diseases. We outline current unresolved challenges to the successful application of stem cell therapies in humans and propose that the baboon model in particular affords a number of traits that render it most useful for preclinical studies designed to overcome these challenges.

Contents

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1. Introduction

PD is a neurodegenerative disorder characterized by the selective loss of dopamine-producing neurons in the substantia nigra pars compacta (SNc) (Carlsson, 1959; Ferri et al., 2007). Rigidity, postural instability, bradykinesia, and resting tremor are the cardinal symptoms (Parkinson, 1817; Dauer et al., 2002), but 50–80% of patients with PD also suffer cognitive impairments such as dementia (Litvan et al., 2012; Hely et al., 2008), personality changes including depression, anxiety, and passivity (Fahn, 2010), and other non-motor symptoms such as sleep irregularity, incontinence, constipation, and fatigue, which typically persist despite treatment (Chaudhuri and Quinn, 2006). Symptoms emerge when approximately 50–60% of the SNc neurons are lost, corresponding to an 80–85% deficit in dopamine levels within the striatum (Wirdefeldt et al., 2011). By the time of death, typically 70–90% of the SNc neurons have been lost (Davie, 2008; Bernheimer et al., 1973; Riederer and Wuketich, 1976).

There are no curative agents for PD, and all available treatments target only the symptoms of the disease. Stem-cell based therapies represent a novel and promising approach to mitigate this disease, however the efficacy and safety of this approach must be optimized prior to its introduction into the clinic including the use of relevant animal models. Due to their close phylogenetic proximity to humans, nonhuman primates (NHPs) provide the most accurate models for such preclinical studies. Of particular relevance to transplantation of stem cell-derived neurons into the brain for the treatment of Parkinson's disease (PD), NHPs accurately mimic key neuroanatomical, neurophysiological, immunological, and genetic features of humans. Among NHP species available for use in biomedical research, the baboon offers several specific characteristics that render it the most promising NHP model for studies of cell-based therapies for PD.

Currently, dopamine replacement therapy is the most common treatment for PD (Tarsy, 2015). The immediate precursor to dopamine, L-dopa, is administered to patients because dopamine itself is incapable of crossing the blood brain barrier (Carlsson, 1959). However, L-dopa induces dyskinesia (Calabresi et al., 2010), increased coronary artery disease (Rogers et al., 2003), emesis in humans (Tarsy, 2015; Bieger et al., 1977; Sanger and Andrews, 2006), and some suggest it accelerates neuronal degeneration (Parkinson Study, 2000; Whone et al., 2003; Group, 2002). More recently, deep brain stimulation of the subthalamic nucleus, globus pallidus, or pedunculopontine nucleus has been used to treat PD (Kumar et al., 1998; Stefani et al., 2007). While deep brain stimulation has proven effective for eliminating some of the motor symptoms of PD, it has shown limited capacity to reduce non-motor symptoms (Fasano et al., 2012). It also does not effectively treat axial motor deficits such as postural instability, and the efficacy of deep brain stimulation declines as the disease progresses (Kleiner-Fisman et al., 2003).

As an alternative to dopamine replacement therapy and deep brain stimulation, PD may be treated by replacing lost neurons with neural tissue derived from progenitor cells. Prior to the advent of pluripotent stem cells, clinicians attempted to treat PD by transplanting cells derived from a variety of heterologous tissue sources into the striatum (Bjorklund and Kordower, 2013). Fetal ventral mesencephalon tissue demonstrated the most success in preclinical studies in rodents, but ultimately failed to significantly reduce parkinsonism in double-blind clinical trials (Freed et al., 2001, 2011; Olanow et al., 2003). There are at least three factors potentially culpable for the failure of previous human clinical trials of cell-based transplantation therapy for PD: 1.) the use of a heterogeneous cell population as a tissue source, 2.) transplanting tissue to a heterotopic graft site, and 3.) the lack of an optimized immunosuppressive regimen (Bjorklund and Kordower, 2013; Lindvall, 2013).

The discovery of pluripotent stem (iPS) cells, which are derived from a patient's own cells, provided an avenue to potentially mitigate immune rejection while simultaneously circumventing the ethical hindrances of using tissues from aborted fetuses. There are a number of studies reporting the ability to differentiate iPS cells into dopamine neurons and subsequently transplant those neurons into rodent brains (Xi et al., 2012; Morizane et al., 2013; Sundberg et al., 2013; Hallett et al., 2015). Although these studies used tissues derived from the host, results demonstrating tolerance of the grafts by the host immune systems are inconsistent (Morizane et al., 2013; Hallett et al., 2015; Soldner et al., 2011; Guha et al., 2013; Araki et al., 2013; Kaneko and Yamanaka, 2013; Kruse et al., 2015; Itakura et al., 2015; Xian and Huang, 2015). Further, as mouse models of PD typically do not display non-motor symptoms (Table 1), these studies were unable to test the ability of stem cell-derived tissue grafts to treat all deficits associated with the disease. Nevertheless, these studies did demonstrate that an autologous dopamine neuron graft is capable of significantly reducing the motor defects in rodents whose midbrain dopamine neurons had been genetically or pharmacologically lesioned.

More recently, work has been performed in the NHP species, *Macaca fasicularis* (the crab-eating macaque), in which autologously transplanted iPS-derived dopamine neurons were able to survive and restore motor deficits for up to 2 years (Hallett et al., 2015). However, the degree to which studies investigating immune tolerance in *Macaca fasicularis* are able to accurately predict outcomes in humans remains a question (see Section 3 of this review). Further, while some non-human primate species have been shown to display non-motor symptoms after MPTP treatment (Hantraye et al., 1996), the ability for iPSC-derived tissue grafts to restore the non-motor deficits in MPTP treated monkeys remains untested. Therefore, questions still remain as to the safety and efficacy of cell-based therapies for PD. Clinical trials have not yet been attempted in humans (Freed et al., 2011), but the inconsistent results of animal studies conducted to date exemplify the need for further, more informative NHP preclinical studies to optimize the safety and efficacy of cell-based therapies for PD.

The possibility of a cell-based replacement approach based on derivation of patient-specific iPS cells (Takahashi et al., 2007) and the subsequent directed differentiation of these cells into transplantable dopaminergic neurons (Soldner et al., 2009) has engendered renewed optimism that an effective cell-based treatment for PD can be developed. iPS cells circumvent the ethical impediments that accompany the use of tissues derived from aborted fetuses (Freed et al., 2001; Olanow et al., 2003, 1996), or from human embryos as would be required for an embryonic stem cell based approach (McHugh, 2004). However, several technical issues surrounding the development of an optimal cell-based protocol for the treatment of PD remain largely unresolved, including 1.) the determination of an optimal target graft site, 2.) the identification and purification of the appropriate neuronal subtype to be transplanted, and 3.) determination of an optimal immunosuppressive regimen necessary to the extent needed to support an autologous transplantation approach. Additionally, long-term studies must be conducted to interrogate both the immunogenic and tumorigenic potentials of the transplanted cells, as well as to assess the full range of therapeutic