Genetically Modified Cells as a Source for Grafting in Parkinson’s Disease

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1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disease and affects almost 1% of the population above the age of 50. PD was first described by James Parkinson in 1817. His essay on the “Shaking Palsy” reported the major symptoms of the disease, such as bradykinesia, resting tremor, and muscular rigidity (Parkinson, 2002). Most patients exhibit vegetative disturbances, with up to a third showing significant cognitive dysfunction (Lang and Lozano, 1998a, b), and almost 40% of PD patients are affected by depression (Oertel et al., 2001). The most conspicuous neuropathologic finding in PD is the progressive loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNC).

In the mammalian ventral midbrain, DA neurons can be found in three different regions, the SNC, the ventral tegmental area (VTA), and the retrorubral field. DA neurons of the VTA project to the ventromedial striatum and cortical area and form the mesolimbic pathway, which is involved in emotional behavior and motivation. DA neurons in the SNC project to the dorsolateral striatum and release DA, an important neurotransmitter which controls movement. Thus, the loss of DA neurons of the SNC leads to a reduction of striatal DA levels (Agid, 1991), that is responsible for some of the cardinal symptoms of Parkinson’s disease.

Currently, there is no treatment that can prevent or retard progression of the disease. Since the late 1960s, the main approach to treating PD has been the pharmacological alleviation of the symptoms caused by the striatal

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DA deficit. Although pharmacotherapy using L-dihydroxyphenylalanine (L-DOPA) or DA receptor agonists is effective in alleviating the symptoms of PD in early stages of the disease, chronic DA therapy is limited by disease progression and the development of therapy-related motor complications, such as dyskinesias (involuntary movements) or partly unpredictable motor fluctuations which significantly affect the patients quality of life (Brotchie et al., 2004; Miyawaki et al., 1997 and see Chapter 3).

One promising treatment option for PD is the restoration of the lost dopaminergic neurons by grafting immature embryonic ventral mesencephalic neurons (Olanow et al., 1996; Hauser et al., 1999; Madrazo et al., 1988; Lindvall et al., 1988, 1990, 1994; Björklund and Lindvall, 2000). Grafting experiments have been performed in animal models of PD where the nigrostriatal dopaminergic system is destroyed, either by 6-hydroxydopamine (6-OHDA) in rats or by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in monkeys, and have shown that grafted dopaminergic neurons can survive, reinnervate the lesioned striatum, and improve motor function. Grafted dopaminergic neurons are active and can restore baseline DA synthesis (for review see Björklund, 1992, 2003).

DA neurons derived from human fetal tissue have been transplanted into 350 patients worldwide. The transplanted cells survive, function and partially reverse motor deficits in PD patients (Björklund et al., 2003 see Chapters 5 and 6), although there are concerns regarding possible side effects connected with transplants (Freed et al., 2001 see Chapters 6 and 10).

There are clearly major limitations related to the collection of fetal tissues. Differences in donor age may lead to heterogeneity of transplants, and the shortage of embryonic donor tissue prevents that this therapy is available for a larger number of patients (see Chapter 8). Therefore alternatives to using primary DA neurons from fetal tissue are sought. The ideal cell for transplantation in PD can be expanded indefinitely and produced on a large scale and is capable of differentiating into neurons that extend axons, form synapses, and release DA in a regulated fashion (see Chapter 12). Stem cells are such undifferentiated cells that have high proliferative potential, generate a wide variety of differentiated progeny, possess the capacity for self-renewal, and retain the multi-lineage potential over time (Gage, 2000). Also, stem cells can be genetically modified to generate DA neurons.

In this chapter we focus on genetically modifying cells to release DA and on the generation of DA neurons from stem cells.

2. Engineering Cells To Produce Dopamine

2.1. Ex vivo Gene Therapy Using Cells Genetically Modified To Release Dopamine

The most direct way to get DA production within the brain may be to use gene therapy to deliver the rate-limiting enzyme of DA synthesis, tyrosine