Developing Novel Cell Sources for Transplantation in Parkinson’s Disease

Nicolaj S. Christophersen, Ana Sofia Correia, Laurent Roybon, Jia-Yi Li, and Patrik Brundin

ABSTRACT

Developing dopaminergic (DAergic) neurons that originate from aborted human embryos have been implanted into the brains of patients with Parkinson’s disease (PD) and, in some cases, have successfully restored function. However, there are insufficient numbers of cells available to allow this therapy to become widely used. The limited amount of tissue from embryos may be circumvented by the use of cell lines that can be expanded in vitro for banking, then differentiated into DAergic neurons just prior to implantation into patients. Today, there are four main sources for such cell lines with future potential for banking and cell therapy for PD: human embryonic stem cells, human neural stem cells, human genetically immortalized stem/progenitor cells, and human adult-derived non-neural stem cells, such as bone marrow–derived stem cells. Currently, it is not possible to utilize these cell sources therapeutically for PD. The primary reasons are because it has not been feasible to effectively differentiate these cells into DAergic neurons and because the stability of phenotypic expression has been variable. This chapter describes methods to generate cells suitable for transplantation in PD in the future. The development of novel cell sources is described, along with an overview of the various types of stem cells that are suitable for grafting in PD.

Key Words: Parkinson; transplantation; dopamine; embryonic stem cells; neural progenitor; differentiation; immortalization.

INTRODUCTION

In the central nervous system, the most abundant source of dopaminergic (DAergic) cell bodies is located in the midbrain, mainly in the substantia nigra pars compacta (SNpc), the ventral tegmental area, and the retrorubral
field. These DAergic neurons extensively innervate the forebrain (e.g., projections to the caudate nucleus, putamen nucleus accumbens, olfactory tubercle) and several cortical and limbic regions, including the amygdala, lateral septum, and ventral hippocampus. The basic organization of midbrain DAergic neurons and their projections is consistent across most mammals (1,2).

The DAergic projections originating in the midbrain and innervating the striatum are the most extensively studied catecholamine neurons, partly because the degeneration of DAergic neurons in the SNpc is one cause of the motor dysfunction present in Parkinson’s disease (PD). This disorder is characterized by tremor, rigidity, hypokinesia, and postural instability. Levodopa treatment initially provides marked symptomatic relief; however, within 5–10 yr, most patients exhibit a gradual loss of efficacy taking levodopa that is associated with the appearance of involuntary movements (dyskinesias; 3).

**Cell Therapy for PD: Proof of Concept**

Both neural transplant studies performed in animal PD models and clinical grafting trials have suggested that cell replacement therapies may be effective in treating PD. Proof of this concept was observed in open-label trials more than a decade ago, when transplantation of human embryonic ventral mesencephalic tissue containing DA neurons was shown to be an effective therapy (4–6). The strategy has been to replace the population of degenerated DAergic neurons with neurons harvested from a donor at an early stage in development, when the cells are still dividing and able to grow processes to their appropriate targets in an adult host brain. This strategy is particularly suitable to explore in PD, since its main pathology is relatively focused on the nigrostriatal DAergic system (i.e., a specific neuronal population within a restricted area of the brain). The classical biochemical deficit in PD results from the loss of DAergic neurons in the SNpc. However, there is also degeneration of the acetylcholine and noradrenaline systems innervating the forebrain (7). This neuropathology may contribute to cognitive and other nonmotor features of this disease, some of which are relatively unresponsive to DAergic replacement therapy (8). Grafts specifically designed to replace the loss of DA in the striatum only treats the core pathology of PD. Nevertheless, this may be sufficient to alleviate the most disabling symptoms.

Thus far, over 300 patients worldwide with PD have received transplants of primary human embryonic tissue that is rich in DAergic neurons. Clinical improvements have been reported for up to 10 yr after transplantation surgery (9,10).