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Stem Cells and Parkinson's Disease: Toward a Treatment, Not a Cure

Clive Svendsen[1,*]
[1]Waisman Center, University of Wisconsin-Madison, 1500 Highland Avenue, Madison, WI 53705, USA
*Correspondence: cnsvendsen@wisc.edu
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Early clinical trials designed to treat Parkinson's disease by transplantation of fetal tissue containing dopamine neuron precursors yielded promising results, but the approach retains several limitations. Multiple recent papers describe longer-term outcomes in these patients, and two additional studies offer novel approaches that may lead to autologous sources of transplantable dopamine neurons.

The first clinical trials that used dopamine neuron replacement therapy for Parkinson's disease (PD) were carried out in Sweden almost 20 years ago by transplanting aborted fetal brain tissue into the brains of PD patients (Lindvall et al., 1990). Remarkably, the transferred tissue harbored immature dopamine neurons that integrated into the striatum, produced dopamine, and in some cases were able to replace drug treatments. However, initial optimism faded when subsequent double-blind trials revealed less substantial effects and a few patients developed dyskinesias, or abnormal movements (Olanow et al., 2003; Freed et al., 2001).

Today, only a few clinical trials are still ongoing as the field holds its breath and waits for the answers to many technical questions. Is there an alternative to using fetal tissue? Will the transplanted cells always be susceptible to rejection? Will grafts succumb to the disease process that killed the endogenous dopamine neurons? Can troublesome dyskinesias be avoided? Can dopamine neuron transplants really provide a cure in a complex disease like PD? Five new papers address some of these issues and are the focus of this article.

The use of fetal tissue as a cell source for clinical transplantation is not very practical, as developing dopamine neurons are rare and only available from exactly 8-week-old embryos. Cells from younger donors will not be patterned correctly, and older cells will not survive. In the early 1990s, researchers began to ask whether stem cells might offer an alternative. It quickly became evident that, while human cells isolated from the fetal tissue used in clinical transplantation studies could be expanded in culture and survive transplantation into rodent models of PD, they failed to generate significant numbers of dopamine neurons when compared to primary tissues (Svendsen et al., 1996). In a seminal publication by McKay and colleagues, this problem was overcome by using mouse embryonic stem cells (ESCs) as a starting source. Unlike their fetal counterparts, ESCs produce large numbers of functional dopamine neurons that, when transplanted, can restore function in rodent models of PD (Kim et al., 2002).

This exciting work on ESCs has now been extended in two important ways. First, Studer and colleagues derived murine embryos via nuclear transfer using donor fibroblasts isolated from mice with experimentally induced PD (Tabar et al., 2008). The resulting blastocysts were used to generate ESCs, which were differentiated into dopamine neurons and transplanted back into the original fibroblast donor mice. Importantly, this study observed improved graft survival and functional recovery when autologous ntESCs were transplanted, suggesting that using exactly matched cells may reduce immune rejection. In an independent, but related, study, Jaenisch and colleagues bypassed the need for nuclear transfer with induced pluripotent stem (iPS) cells derived by the enforced expression of four transcription factors in adult fibroblasts (Yamanaka, 2007). Existing murine iPS cell lines were differentiated into neural lineages and then dopamine neurons by using established techniques (Wernig et al., 2008). The resulting cells were subsequently transplanted into a rat model of PD, where they elicited functional improvement. In both of these proof-of-principle studies, the authors conclude that dopamine neurons produced from either cloned mouse embryos or reprogrammed skin cells are able to functionally integrate into the brain and release dopamine—perhaps the best obtainable evidence that neurons derived using these methods can mature appropriately.

Of course, translating these exciting mouse studies to human PD patients is

the next challenge. Certainly, the opportunity to use autologous cells to generate dopamine neurons is appealing, as it would yield transplants with very low rejection levels. Indeed, while human ESC lines have not yet been established by using nuclear transfer techniques, recent observations that iPS cells can be generated from human fibroblasts is encouraging (reviewed in Jaenisch and Young, 2008). However, the logistical challenge of having to produce individual, patient-specific cell lines is daunting, particularly in the case of nuclear transfer, given the number of egg donors that would be required. Furthermore, to date, iPS cell derivation requires the insertion of multiple genes and, when combined with the poorly understood genomic alterations associated with reprogramming, raises important safety issues. Finally, while many PD patients do not bear known mutations for PD, they may still exhibit novel, unidentified susceptibility gene profiles. Thus, an autologous transplant might be at risk of an accelerated course of pathological changes relative to cells from a healthy donor.

Beyond the question of the source of dopamine neurons for transplantation, two additional reports of patients receiving fetal tissue grafts address the long-term potential of this therapy paradigm. The studies reveal that some of the surviving dopamine neurons exhibit pathological changes associated with PD (Li et al., 2008; Kordower et al., 2008). This raises the fascinating possibility that the aging, diseased environment transmits a toxic signal to the grafted neurons, in which case transplanted cells from any source would be equally threatened. However, while these results demonstrate that grafted cells can exhibit PD pathology, only a few neurons appear to be affected. In addition, a third study of other grafted PD patients did not observe any pathology in the transplanted dopamine neurons (Mendez et al., 2008). Overall, while the recent human studies offer insight into the potential spread of PD pathology, the jury is still out on the relevance of a few aberrant neurons to this therapeutic approach.

Together, it seems that these five studies leave us with an added appreciation for the remaining hurdles that face dopamine neuron replacement therapies for PD. Stem cells certainly offer an ideal source of dopamine neurons, and these latest studies imply that autologous cells may one day be available for transplant therapies, provided the diseased host environment does not prevent their function. But perhaps the taller hurdles lie ahead. The mechanisms underlying dyskinesias that appear in some transplant patients must be elucidated to increase safety. Stem cells may be used to tackle this problem as well, if more defined dopamine populations can be produced, or engineered by using inducible promoters to control dopamine release. In this way, the patient could take a drug to activate dopamine production for better control of neuronal activity. The next hurdle is higher still. Most current transplant strategies for PD deposit the cells ectopically in the striatum, a forebrain structure. While convenient for dopamine neurons to connect to their target, the location of the endogenous, damaged dopamine neurons is buried deep in the midbrain, many centimeters away. In order to restore the original circuit, dopamine neurons must be engrafted back into the midbrain and then undergo long-distance axon regeneration to targets in the striatum. If possible, this approach has the potential to restore physiologically relevant input to the new dopamine neurons and perhaps provide the normal fine control over dopamine release that characterizes this system. However, extensive long-distance axonal outgrowth into the adult brain has been difficult to achieve in other studies.

The final hurdle facing dopamine neuron replacement strategies is that PD pathology is not restricted to the loss of dopamine neurons. Many other systems degenerate in PD patients and may need to be addressed in addition to re-establishing dopamine signals in the brain. But dopamine replacement may be only part of the story. Stem cells can also produce astrocytes, which are able to modulate synaptic transmission, toxic glutamate levels, and the blood-brain barrier function. They can also be genetically modified to release powerful drugs within specific brain regions. So, while cures based on dopamine neuron transplantation may not be around the corner, stem cells offer many new potential avenues of therapy for PD patients that may compliment current treatments.

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