

Inhibition as a Transplant-Mediated Therapy: A New Paradigm for Treating Parkinson's?

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DOI 10.1016/j.stem.2010.02.003

In this issue of *Cell Stem Cell*, [Martínez-Cerdeño and colleagues \(2010\)](#) transplant interneuron precursors from the MGE into the striatum of a rat model of Parkinson's disease and observe a 5% increase in the endogenous GABAergic interneuron population resulting in behavioral benefits in both lesioned and wild-type animals.

One in eight hundred individuals in the Western world suffers from Parkinson's disease (PD), which predominantly results from dysfunction in dopaminergic, neuromelanin-containing cells of the substantia nigra pars compacta (SNc). Although dopaminergic cells are disproportionately affected in PD, the syndrome more generally results in dysregulation of the processing of information by the basal ganglia. In recent years, direct treatment of PD has been attempted with transplantations to restore dopamine levels. The first human trials with adrenal chromaffin cells, which produce and release substantial quantities of catecholamines, gave promising, but unfortunately not very reproducible, results ([Drucker-Colin and Verdugo-Diaz, 2004](#); [Freed et al., 1981](#)). Others have decided to strike the problem at its core by transplanting embryonic or partially differentiated SNc cells in different brain regions ([Bjorklund and Stenevi, 1979](#)). For this approach to succeed, axons from the transplanted cells need to find their way to the striatum where dopamine exerts its action on both GABAergic medium spiny projection neurons and interneurons. To overcome this challenge, an alternative approach is to transplant the dopamine neuronal precursor cells directly into the striatum ([Freeman et al., 1995](#); [Lindvall et al., 1994](#)).

In this issue, [Martínez-Cerdeño et al. \(2010\)](#) undertook a variation on this approach in an attempt to restore some of the motor deficits observed in 6-OHDA (6-hydroxydopamine) SNc-lesioned animals, a widely used model of PD. Instead of trying to restore dopamine levels by

introducing new dopaminergic neurons, the authors transplanted GABAergic precursor cells into the striatum. Forebrain GABAergic cells have been shown to originate embryonically from the ganglionic eminences of the ventral telencephalon, which based on anatomical and gene expression criteria have been subdivided into three anlagen, the medial, lateral, and caudal ganglionic eminences (MGE, LGE, and CGE, respectively) ([Batista-Brito and Fishell, 2009](#)). Of these regions, the MGE is known to produce a large percentage of striatal GABAergic interneurons, which have the remarkable ability to migrate widely even after transplantation within the postnatal forebrain ([Wichterle et al., 1999](#)). Therefore, although the idea of introducing inhibitory GABAergic neurons may seem counterintuitive, if one thinks of PD as a network dysfunction ([DeLong and Wichmann, 2007](#)), the new methodology is highly intriguing.

In testing the inhibitory approach, [Martínez-Cerdeño et al. \(2010\)](#) dissected out MGE-derived precursor cells from E14.5 rat brains and transplanted them into the striatum of the 6-OHDA-lesioned rats. Although 25% of the cells within these grafts differentiated into oligodendrocytes, the remainder became neurons. Remarkably, MGE grafts directed into the striatum produce no astrocytes, despite the observation by the authors that the same cells transplanted into the subthalamic nuclei gives rise solely to astrocytes. Moreover, although only 1% of the grafted cells survived in the striatum after 1 year, those present differentiated into morphologically and electrophysio-

logically mature interneurons of the three major subtypes found in the striatum, namely CR⁺, PV⁺, and SOM⁺ cells ([Tepper and Bolam, 2004](#)), all of which have been shown to originate from the MGE at embryonic stages. Even more remarkably, even though the surviving transplanted interneurons accounted for only about 5% of the total endogenous GABAergic interneuron population, they were sufficient to provide functional recovery in the lesioned animals, as assessed by behavioral and motor activity. The authors show that the interneurons integrated into the host circuitry by receiving and forming de novo synapses and hence they hypothesize that it is the transplant-mediated reorganization of the basal ganglia network that directly results in the functional recovery observed. By contrast, when the same donor cells were transplanted into the subthalamic nuclei, they failed to disperse, produce neurons, or provide therapeutic improvement of PD-like symptoms.

Why would MGE transplants into the striatum give such robust results? Do the interneurons or the oligodendrocytes generated provide trophic support for residual dopaminergic fibers or, as [Martínez-Cerdeño et al.](#) hypothesize, is the effect due to the direct electrical impact of the grafted interneurons on the network? Although one can speculate upon any number of convoluted circuit rearrangements to which the transplanted MGE cells might contribute, there are two simple mechanisms by which inhibition provided by grafted interneurons could lead to the observed behavioral changes. Information coming into the

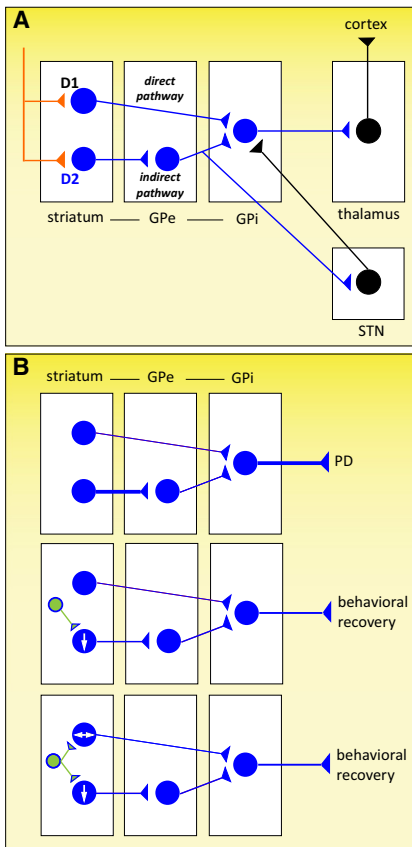


Figure 1. Modeling the Potential Impact of Striatum-Grafted MGE Precursors on a Rat Model of Parkinson's Disease

(A) A simple diagram of the flow of information through the medium spiny neurons of the basal ganglia consisting of the striatum, the external globus pallidus (GPe), and the internal globus pallidus (GPi), and including the modifying influence of the subthalamic nucleus (STN). Dopamine input (orange) is delivered to both the direct and indirect pathways. The direct pathway leads to a net activation of the thalamus, whereas the indirect pathway leads to a net decrease and thus less motor activity. D1, dopamine type 1 receptor (excitatory); D2, dopamine type 2 receptor (inhibitory). Black projections indicate excitatory connections, and blue projections represent inhibitory.

(B) These three panels illustrate how basal ganglia circuitry is altered in Parkinson's disease (PD) (top), and two possible ways by which grafted GABAergic interneurons could hypothetically rescue proper function of this network (middle, bottom). The green cells represent EGFP-positive grafted interneurons and their possible contributions to restoration of basal ganglia network function. Note that line thickness represents strength of connection.

striatum from the cortex and the dopaminergic neurons of the SNc segregates into two parallel routes, generally referred to as the direct and indirect pathways (Figure 1A). Dopamine is excitatory on medium spiny neurons of the direct pathway but inhibitory on those contributing to the indirect pathway. Because of this distinction, as well as the differential involvement of other inhibitory and excitatory elements in the two pathways, activation of the direct pathway results in increased thalamic and hence motor activity, whereas activation of the indirect pathway decreases it. In PD, the direct pathway is less excited whereas the indirect one is less inhibited and as a result the output of the internal globus pallidus (GPi) onto the thalamus is increased overall (Figure 1B, top). This elevation in activity ultimately culminates in the rigidity and constraint in voluntary movement characteristically observed in PD patients.

Because the transplanted MGE neurons alleviate the motor symptoms of PD animals, their net effect must be to decrease the inhibitory output of the GPi to the thalamus. This result could be accomplished either by preferentially inhibiting the indirect pathway (Figure 1B, middle), and thus increasing GPi inhibitory output, or by providing indiscriminate inhibition to both the direct and indirect pathways (Figure 1B, bottom). For the latter to be effective, one must imagine that the direct pathway in conditions of PD already has such a low level of excitability as to make it nonfunctional, making its further inhibition irrelevant.

Although many questions remain unanswered, the results of Martínez-Cerdeño et al. suggest that there might be alternatives not only to the transplantation of dopaminergic precursors into the brain but also the general efforts for dopamine replenishment in PD patients. It is important to remember that animal models, and the behavioral tests used to assay

them, do not always reproduce human symptoms and responses. However, if the approach outlined by Martínez-Cerdeño and colleagues proves to be effective, it offers a number of attractive advantages over the more traditional transplantation of SNc DA neurons. First of all, fewer cells are probably needed for transplantation (i.e., GABAergic interneurons versus SNc cells). Second, the cells transplanted are of a kind normally found in the striatum. Finally, the interneurons have been shown to have a remarkable ability to disperse, integrate, and persist within the striatum. Thus, it may be that a minimal impact on GABAergic activity in the striatum, 5% in the case of Martínez-Cerdeño et al., is sufficient to provide an effective therapy for PD.

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