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Endogenous repair mechanisms enhanced in Parkinson's disease following stem cell therapy

Eleonora Napoli

Abstract:

This mini-review highlights the innovative observation that transplanted human neural stem cells can bring about endogenous brain repair through the stimulation of multiple regenerative processes in the neurogenic area (i.e., subventricular zone [SVZ]) in an animal model of Parkinson's disease (PD). In addition, we convey that identifying anti-inflammatory cytokines, therapeutic proteomes, and neurotrophic factors within the SVZ may be essential to induce brain repair and behavioral recovery. This work opens up a new area of research for further understanding the pathology and treatment of PD. This paper is a review article. Referred literature in this paper has been listed in the references section. The datasets supporting the conclusions of this article are available online by searching various databases, including PubMed. Some original points in this article come from the laboratory practice in our research center and the authors' experiences.

Keywords:

Central nervous system disorders, endogenous neurogenesis, Parkinson's disease, regenerative medicine, stem cell therapy

Introduction

Over the past 30 years, clinical trials of cell therapy for treatment of Parkinson's disease (PD)^[1] have created interest in the scientific community and in public.^[2,3] Indeed, cell transplantation has emerged as a promising new technology within science largely due to its direct clinical application.^[4-6] PD was a logical choice to test the safety and efficacy of cell therapy due to its well-defined pathology and most importantly the possibility of employing a straightforward therapeutic approach through dopaminergic cell replacement.^[7-11] A promising study in the 1980s including fetal dopaminergic cells transplanted into PD patients^[12-15] resulted in the successful survival of the cells as well as reintegration with the host cells.^[13] However, despite these initial results minimal improvements, that

lessened over time following transplantation, were recorded in the transplanted PD patients^[14-17] and a few even displayed significant (though debated) side effects^[18,19] such as worsening dyskinesias.^[20] Even with the lackluster outcomes of the treatment in PD, the promise of cell therapy has been researched in other brain diseases^[21-24] including stroke,^[25,26] traumatic brain injury,^[27] and Huntington's disease.^[28,29] Undoubtedly, for cell therapy treatments for central nervous system disorders to reach the clinic, treatments should be optimized to ensure safety and efficacy.

Testing Stem Cells in Animal Models of Parkinson's Disease

Using an animal model of PD,^[1] a study investigated the therapeutic benefits of human neural stem cells (hNSCs), an alternative tissue source which may prove critical in bypassing the ethical issues surrounding fetal cells. Due to the cardinal pathologic feature of the disease, laboratory and clinical studies of PD

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have thus far been focused on the recovery of nigrostriatal dopaminergic pathways following cell transplantation. This forward thinking group decided to parallel the study of the specific brain dopamine system with the assessment of the subventricular zone (SVZ), a major neurogenic area (the hippocampal subgranular zone [SGZ] being the other stem cell-enriched brain area). This study may have unearthed a possible regenerative pathway in PD with the discovery that the SVZ mounts an endogenous repair mechanism following injury. The key role of the SVZ in the functional recovery of dopamine-depleted animals that received hNSC transplants was evaluated using a suite of effective readouts including behavioral tests, imaging, immunohistochemical assays, and proteomics. Compared to a lesion controlled adult mouse, the group that received 6-hydroxydopamine (6-OHDA)-induced dopamine lesions followed, 7 days later, by transplantation of undifferentiated hNSCs performed better in motor and cognitive tasks. The improvement in behavior was coupled by changes in the proteome profile, neurotrophic factor secretion, and cytokine levels in the SVZ, even in the absence of significant proliferation of the transplanted hNSCs. These findings suggest that the hNSCs did not contribute directly to the functional improvement observed in transplanted parkinsonian animals, which was instead conceivably achieved by stimulation of the endogenous stem cells residing in the neurogenic SVZ.

This scenario advances the idea that transplanted hNSCs, or stem cells, could interact with the SVZ through a bystander mechanism that promotes therapeutic effects. Going against the tide of PD research, this concept challenges the conventional dopaminergic cell replacement strategy. Naturally, due to the recognition of the nigrostriatal dopaminergic pathway as the one affected in PD,^[6-10] most studies examining the effects of stem cell therapy have been focusing on this system^[4-6] as a therapeutic target. Functional outcomes for PD cell therapy have thus far relied on the assessment of dopamine-sensitive tasks and shifted the focus to the reconstruction of dopaminergic circuitry as the goal for cell therapy in PD. Thus, dopamine-induced circling behavior has been the main behavioral testing in cell therapy studies of PD animals.^[7,8-10,30,31] The over-reliance on the dopamine depletion pathology and its accompanying symptoms have consequently limited the research area on experimental treatments for PD. When contemplating experimental models of PD, the well-established unilateral 6-OHDA nigrostriatal dopaminergic lesion model has focused the field to a specific and direct cell replacement concept.

Therapeutic Modalities of Stem Cells

Deviating from this long-held dogma of reconstructing the nigrostriatal dopaminergic system, transplanted

stem cells have been shown to propel the long-neglected neurogenic niche, notably the SVZ, to assist in the brain repair process, and its high responsiveness to cell therapy.^[1] Compelling evidence shows that transplantation of the stem cells led to the restoration of the SVZ proteome profile and induced the SVZ to carry out multi-pronged regenerative processes, including the secretion of anti-inflammatory cytokines and a specific set of putative reparative growth factors.^[1]

Based on these paradigm-shifting findings,^[1] many new observations may serve as the basis for future mechanism and optimization studies. An important insight is that undifferentiated hNSCs were comparably effective in lessening PD symptoms as the fetal dopaminergic cells classically used for transplantation in PD. This is of importance, as a major hurdle encountered in the clinical trials of fetal dopaminergic cells is the need to harvest 3–6 fetuses at about 6–9 weeks gestation,^[16,32,33] a requirement that cripples the feasibility of large clinical trials. Similarly, challenging is the possibility to generate a substantial supply of neural stem cells with dopaminergic phenotype from embryonic and induced pluripotent stem cells. The observation that naive, unmanipulated, nondopaminergic hNSCs could create robust functional recovery in PD dodges the requirement of differentiating stem cells into dopaminergic cells.

Another remarkable observation entails the improvement of cognitive performance linked to the hippocampus, the area of the brain responsible for learning and memory,^[34-36] broadening the field of research beyond the SVZ. In this regard, a disrupted communication between the hippocampus and the dopaminergic system has been associated with the cognitive impairment related to PD.^[37,38] The hypothesis is that dopamine segregation in the striatum,^[39] and possibly in the substantia nigra, likely does not fully encompass the synaptic plasticity dysfunctions in PD. Thus, the extension of neurodegeneration to areas beyond the nigrostriatal dopamine pathway, such as the hippocampus, presents a possible new avenue for PD treatment. Due to its hippocampal location, a study that aims at the evaluation of endogenous stem cell fate, proteome, neurotrophic factor, and cytokine profiling in the SGZ has the potential to unveil the mechanism underlying the contribution of the host neurogenic niches to the bystander effects of cell therapy in PD, as previously tried in rat^[40] and primate^[41] models of PD. Altogether, these studies not only highlight the role of the SVZ in the brain repair process in PD but also showed that the reconstruction of the damaged dopaminergic neuronal circuitry is likely crucial for long-term recovery. In this regard, the concept of a cellular biobridge has been advanced as an extracellular matrix formed by the transplanted cells that can transfer the endogenous stem cells from

the SVZ to injured areas separated from the neurogenic region.^[42] Along with the discussed SVZ repair, there is the possibility that the transplanted hNSCs may also utilize a biobridge, which could allow the endogenous SVZ-derived stem cells to be shepherded to the neighboring dopamine-denervated striatum, resulting in the re-establishment of the dopamine-depleted nigrostriatal pathway. In-depth proteomic examination of stem cells and their exosomes,^[43] and the following manipulation of identified lead proteomes, growth factors, and anti-inflammatory cytokines through silencing RNAs or viral vector overexpression may show their fully therapeutic potential in functional recovery of PD.

Conclusion

Transplantation of exogenous stem cells can trigger endogenous brain repair through a myriad of regenerative processes in the host neurogenic niches, including the secretion of anti-inflammatory cytokines, proteomes, and neurotrophic factors.^[44,45] The mechanism underlying the role of these therapeutic molecules and the extent to which they reach the striatum and substantia nigra after the hNSC-mediated SVZ stem cell propagation is paramount in optimizing stem cell-based therapy for targeting the neurogenic niche in treating PD.

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Conflicts of interest

There are no conflicts of interest.

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