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RESEARCH HIGHLIGHT

Autologous Transplantation for Parkinson's Disease Patients: Feasibility and Challenge

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Parkinson's Disease (PD), second only to Alzheimer's disease, is a neurodegenerative disease, most commonly occurring in people over the age of 65 years and is mostly caused by loss of dopamine neurons [1]. Clinically, motor symptoms such as resting tremor, motor retardation, muscular rigidity, and disturbance of postural balance are the main symptoms, followed by non-motor symptoms such as cognitive impairment, autonomic nervous system dysfunction, depression, and sleep disorder [2]. In 2016, >6.1 million people were affected with PD globally, 2.4 times the number in 1990. The large number of affected people, coupled with the high mortality and disability rates, has placed a great burden on society [3]. Traditional treatment methods mainly include drugs and surgery and are supplemented by physical therapy. Drugs commonly used include levodopa, dopamine receptor agonists, and monoamine oxidase B inhibitors. Surgical treatment mainly includes deep brain stimulation, focused ultrasound ablation, and placement of a levodopa infusion pump. However, medication or surgical treatment only controls the symptoms and not the progression of the disease [4]. New treatments are urgently needed.

A recent study demonstrated that the transplantation of autologous induced dopamine progenitor cells derived from pluripotent stem cells in a patient with PD [5]. The researchers transformed skin fibroblasts from the patient into induced pluripotent stem cells, differentiated them into dopamine precursor cells *in vitro*, performed a series of identification and related experiments, and finally completed a pilot study of autologous cell transplantation therapy [6]. The patient was a 69-year-old man with a 10-year history of PD. His symptoms of tremors and postural balance disorder were increasingly serious and levodopa and other drugs were ineffective. With the patient's informed consent and approval of the US Food and Drug Administration, he received personalized dopamine neural precursor cell autograft transplantation therapy. Before the clinical trial, neurologists performed neurological examinations and evaluations, followed by a stereotactic injection into the left putamen, and 6 months later, into the right putamen. CT was performed immediately after the injections and no bleeding was found. A series of detailed neurological examinations and evaluations were performed over 24 months after the injections, and graft survival was assessed by 18F-DOPA PET. After clinical evaluation, the patient had no adverse events or dyskinesias during follow-up. Scores on the MDS-UPDRS, part III (to assess parkinsonian motor signs), after overnight withdrawal of dopamine replacement therapy ("off") were 43 at 4 weeks after the first implantation and 33 at 24 months. The scores at the peak dose of dopamine

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replacement therapy ("on") were 38 at the time of implantation, and 29 at 24 months. PDQ-39 scores (to assess parkinsonian disease-related quality of life; lower scores indicate better quality) were 62 at the time of implantation, and 2 at 24 months. Certainly, he did not follow the usual worsening trajectory of PD patients and showed some evidence of small improvements. The use of an autologous source rather than human embryonic stem cells or other allogeneic tissues has the major theoretical advantage of removing the need for immunosuppression. The results greatly encourage researchers in cell replacement therapy, and promote cell transplantation therapy to the clinical stage; this is a milestone of progress.

In the past few decades, cell transplantation therapy has been advancing. In 1998, Thomson reported embryonic stem cell lines from human blastocysts for the first time, and Kazutoshi reprogrammed human skin fibroblasts into induced pluripotent stem cells for the first time in 2007 [7], after which the development of human pluripotent stem cells entered a new era. PD researchers are also constantly exploring and promoting the clinical application of basic stem cell research. In 2011, Sonja differentiated embryonic stem cells into dopaminergic precursor cells through a novel method and greatly improved their quality. These cells were then transplanted into mouse, rat, and monkey models of PD. Eventually, they found that grafts can survive without forming teratomas, and the symptoms in animals improve to some extent after the transplants [8]. In 2017, Tetsuhiro transplanted dopaminergic neural precursor cells derived from induced pluripotent stem cells from healthy people and patients with PD into a monkey model of PD, and after two years of examination and evaluation, found that the transplanted cells were alive, the symptoms were improved, and some markers, including the *Dlk1* gene, may be used to predict the presence of donor cells in good condition [9]. Since then, many institutions have carried out clinical trials of dopaminergic neural precursor cells differentiated from human pluripotent stem cells in the treatment of PD.

Although we are optimistic that such research may bring hope for a cure of PD, the tumorigenicity, immunogenicity, and inherent heterogeneity of cells still pose many problems such as cell source, cell quality, injection method, and the number of transplanted cells, which directly or indirectly affect the efficacy of cell replacement therapy. Quality control is the lifeline of a cell product; how to manage cell transplantation in all kinds of clinical experiments is an urgent problem that needs to be solved. Currently, in China, the issue of registration and approval regulations for clinical trials of similar drugs using stem cells is being explored. As Lindvall emphasized, we should take a rational, scientific, and rigorous approach to the therapeutic effects of clinical trials for PD and continue to optimize the transplantation program [10]. Many colleagues in China who are also doing this kind of work. Let's work together to promote the project.

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Conflict of interest The authors claim that there are no conflicts of interest.

References

1. Li T, Le W. Biomarkers for Parkinson's disease: How good are they? Neurosci Bull 2020, 36: 183–194.
2. Dong D, Xie J, Wang J. Neuroprotective effects of brain-gut peptides: a potential therapy for Parkinson's disease. Neurosci Bull 2019, 35: 1085–1096.
3. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019, 18: 459–480.
4. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA 2020, 323: 548–560.
5. Schweitzer JS, Song B, Herrington TM, Park TY, Lee N, Ko S, *et al.* Personalized iPSC-derived dopamine progenitor cells for Parkinson's disease. N Engl J Med 2020, 382: 1926–1932.
6. Song B, Cha Y, Ko S, Jeon J, Lee N, Seo H, *et al.* Human autologous iPSC-derived dopaminergic progenitors restore motor function in Parkinson's disease models. J Clin Invest 2020, 130: 904–920.
7. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, *et al.* Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007, 131: 861–872.
8. Kriks S, Shim JW, Piao J, Ganat YM, Wakeman DR, Xie Z, *et al.* Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease. Nature 2011, 480: 547–551.
9. Kikuchi T, Morizane A, Doi D, Magotani H, Onoe H, Hayashi T, *et al.* Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. Nature 2017, 548: 592–596.
10. Lindvall O. Balancing expectations for success in stem cell-based clinical trials for Parkinson's disease. Cell Stem Cell 2020, 27: 519–522.