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Enhanced survival of human-induced pluripotent stem cell transplant in parkinsonian rat brain by locally applied cyclosporine

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Abstract:

A major limitation with cell transplantation in patients is the unimpressive number of cells survived. The death of grafted cells involves apoptosis and immunorejection. In this review, we encapsulate the recent preclinical development that improves the survival of grafted cells and mitigates the immunorejection of human-induced pluripotent stem cells (iPSCs) through co-grating nanoparticles-containing cyclosporine A (NanoCsA) in hemiparkinsonian rats. The study supported the notion that NanoCsA allows for long-lasting CsA discharge and limits immunorejection of human iPSC xenograft in a 6-hydroxydopamine Parkinson's disease rat model.

Keywords:

Co-grafts, cyclosporine-A, immunorejection, nanoVeh, nanoparticles, Parkinson's disease, stem cells, trophic factors, Wharton's jelly mesenchymal stem cells, xenografts

Introduction

Parkinson's disease (PD) is the second-most common neurodegenerative disorder of aging. The principal pathology in PD is degeneration of dopaminergic neurons in the ventromesencephalon and reduction of dopaminergic innervation to the striatum. Current pharmacological therapy only provides symptomatic relief and does not stop the disease from progressing.

Cell Transplantation in Animal Models of Parkinson's Disease

Restoration of dopaminergic function or circuit by allogenic grafts has been extensively studied in animal models of PD.^[1-3] The fetal ventromesencephalic cells from rats were transplanted to 6-hydroxydopamine (6-OHDA)-lesioned

rats. These grafted cells survive in the host brain, reduce apomorphine-mediated rotation, and restore dopamine (DA) overflow and clearance function.^[1]

Transplantation of Human Dopaminergic Cells to 6-Hydroxydopamine-Lesioned Rats

Similar to the allogenic grafts, human dopaminergic cells have been grafted to 6-OHDA-lesioned rats.^[4-6] To ensure the survival of xenografts in the host brain, the immunosuppressive agent cyclosporine A (CsA) was used as an adjunctive therapy to avoid xenograft rejection.^[5] Chronic treatment with CsA improved the survival and function of transplanted human fetal ventromesencephalic cells in 6-OHDA-lesioned rats. With the help of CsA, the human fetal dopaminergic grafts can survive in the host striatum for more than

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3 months, reduce the apomorphine-induced rotational behavior, and restore DA release as well as DA clearance in the striatum in hemiparkinsonian rats.^[5] In contrast, without immunosuppressive therapy, most of these grafted cells were rejected by the hosts.

A growing amount of evidence also supports the notion that transplanting human stem cells encourages neuroprotective and reparative effects in PD rat models.^[7,8] Patient-derived induced pluripotent stem cells (iPSCs) can be separated into disease-relevant neurons, which offered a novel and unparalleled platform for *in vitro* modeling. Eventually, they can be developed into therapeutic strategies to treat neurogenerative disorders.^[9] Differentiating between iPSCs and pluripotent stem cells would be favorable because they have great value to be used *in vivo* with transplantation for PD-affected individuals.^[10]

Systemic Cyclosporine Improves the Survival of Human Stem Cells in Rodent Brain

Chronic and systemic immunosuppressive therapy is also needed to improve the survival of grafted human stem cells.^[8] Without immunosuppressants, such as CsA, human Wharton's jelly-mesenchymal stem cells (hWJ-MSCs) or neuronal-primed human MSC transplants were rejected by an inflammatory response in the host brain in rodents.^[11,12] CsA inhibits activation of resident microglia and reduces the phagocytosis of grafted hWJ-MSCs or oligodendrocyte progenitor cells.^[11,13]

Systemic Cyclosporine A Causes Side Effects

Long-term administration of CsA is required to suppress immunorejection of human xenograft in rodent brain. However, systemic and daily use of CsA triggers multiple side effects in the kidney,^[14,15] brain,^[16,17] and other organs.^[18] Because of these damaging side effects, another treatment routine for CsA is needed to keep the graft alive while reducing systemic complications.

Using Nanocyclosporine A to Treat Parkinson's Disease

A recent study^[19] has created a new treatment plan that can quell the immunorejection while still using the established treatment of CsA. This treatment was inspired by their earlier work with a glucagon-like peptide-1 agonist exendin-4 that protected dopaminergic neurons against degeneration, preserved DA levels, and improved motor function in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

mouse model of PD.^[20] A new formulation of exendin 4 (also named PT302) was later designed. Exendin-4 was loaded with a bio-degradable polymer, poly-(D, L-lactide-co-glycolide) microspheres, which provided sustained elevation of exendin-4 for 3 weeks after a single-dose injection in rats.^[21] PT302 significantly increased tyrosine hydroxylase (TH)-immunoreactive in the lesioned substantia nigra and striatum. In this report, a similar method was adopted to create CsA poly-(L-lactide) nanoparticles (NanoCsA). This allowed for the extended release of CsA for more than 40 days *in vitro*. This study was able to establish the principle that co-grafting the NanoCsA enhanced the survival of human iPSCs that were transplanted into rodent brains. Such use of NanoCsA in transplants in animal models of PD represents an entirely new line of research.

Nanocyclosporine A: Suppressing Immunorejection While Releasing Cyclosporine A Locally

The biocompatible NanoCsA that was created in this study was capable of delivering a constant discharge of CsA for a period longer than 6 weeks *in vitro*. The expression of TH (+) cells and the human-specific marker Stem121 increased when the NanoCsA and iPSCs xenografts were transplanted in 6-OHDA-lesioned rats. The data from this study support that NanoCsA co-graft reduces the immunorejection of human iPSCs in 6-OHDA-lesioned rats.^[19]

The beneficial results of human xenografts have been inspected in experimental animals. In order to increase the survival rate of the grafted cells, long-term systematic use of immunosuppressive therapy is required. Through an inflammatory response that takes place in the host brain, the hWJ-MSCs are rejected if no immunosuppressive therapy is applied. When the host animals were treated with CsA, the CsA lowered the phagocytosis of oligodendrocyte progenitor or hWJ-MSCs.^[11] Systemic CsA also increased the amount of human ventromesencephalic grafts that survived and their dopaminergic functions^[5] as well as the survival of hWJ-MSC transplants in the rats.^[22] However, systemic administration of CsA often induces renal and other toxicities.^[14,15,18] Systemic and chronic CsA injection (CsA s.c./iPSCs) reduced body weight and locomotor activity. In contrast, intracerebral NanoCsA/iPSCs did not alter body weight while improved locomotor function in 6-OHDA-lesioned rats. CsA was released locally through NanoCsA near the graft site. A higher frequency of TH and human marker Stem121 immunoreactivity was found in the rats receiving NanoCsA/iPSCs, compared to the rats that got NanoVeh/iPSC. The results from this study support the notion that NanoCsA mitigates the systemic side effects of CsA and immunorejection of the xenografts.

A few studies have indicated that human stem cell transplant produced functional improvement without co-administration of CsA in rodents. For example, transplantation of hWJ-MSCs lowered brain infarction and improved the behavior in rat stroke models without the CsA treatment.^[22] The functional improvement after transplantations may indirectly come from trophic factors in the graft cells.^[23]

To summarize, this study demonstrated the idea that using NanoCsA in a 6-OHDA rat model delivered a long-lasting release of CsA. Furthermore, co-grafting the NanoCsA also lowered the immunorejection of the human iPSC transplants in the host rats [Figure 1]. As a result, it increases the number of cells that survive at the target site.

Connection to Brain Circulation

A major limitation with cell transplantation in patients is the unimpressive number of cells that survive. The death of grafted cells involves apoptosis,^[24,25] immunorejection,^[19,22] and other factors. Several approaches have been employed to improve the survival of grafted cells. For example, systemic administration of a p53 inhibitor, pifithrin-alpha, reduced apoptosis and enhanced the survival of dopaminergic neuronal transplant in hemiparkinsonian rats.^[26] Administration of glial cell line-derived neurotrophic factor (GDNF) increased the spouting of ventral mesencephalic grafts in 6-OHDA-lesioned rats.^[3,27,28] Co-transplantation of NanoCsA locally releases CsA and mitigates immunorejection of grafted iPSCs.^[19]

A central feature in cell therapy of PD is that the transplanted cells need to be carefully targeted. Similar to the co-transplantation of NanoCsA and iPSCs, co-transplantation with GDNF-releasing cells increases the number and sprouting of survival grafted ventral midbrain cells and improves behavioral function.^[29-31] These approaches can be useful for future clinical use.

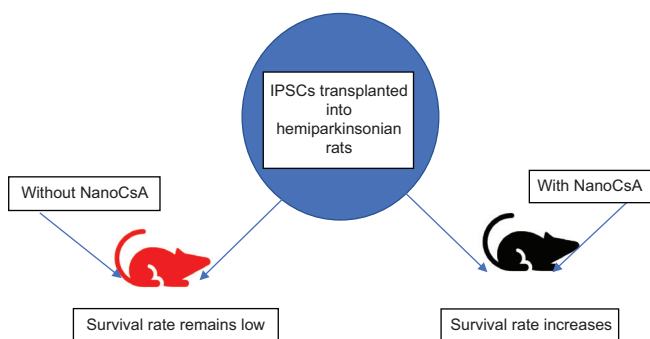


Figure 1: Nanocyclosporine A and graft survival. Treatment with nanocyclosporine A enhances graft survival in an animal model of Parkinson's disease

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Conflicts of interest

There are no conflicts of interest.

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