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A Neuroprotective Microenvironment was Constructed for Dopaminergic Neuron Grafts Using Autologous Treg Cells

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Abstract: *Objective:* To discuss the construction of a neuroprotective microenvironment using autologous regulatory T cells (Treg cells), in order to improve the transplantation survival rate and functional recovery effect of dopaminergic neurons derived from induced pluripotent stem cells (iPSCs) in Parkinson's disease (PD) models. *Methods:* We have elaborated in detail on the current research on animal models of PD: the combined transplantation of autologous regulatory T cells and dopaminergic (DA) neurons derived from induced pluripotent stem cells. *Result:* Co-transplantation of Treg cells can significantly increase the survival rate of dopaminergic neuron grafts, inhibit the host immune response and microglial cell activation, and promote the recovery of motor function in model animals. Treg cells activate the Rac1/Akt signaling pathway through direct cell contact (such as CD47-SIRPA interaction), and secrete anti-inflammatory factors (such as IL-10, TGF-β) and neurotrophic factors, exerting immunomodulatory and direct neuroprotective effects. Drug enhancement of Treg function can further optimize this protective effect. *Conclusion:* I have elaborated in detail on the current research status and clinical feasibility of using autologous regulatory T cells to construct a neuroprotective microenvironment for dopamine neurons transplantation. At the same time, we envisioned the future treatment methods for PD, providing new ideas for research and treatment for PD scholars and doctors.

Keywords: Regulatory T cells; Dopaminergic neurons; Cell transplantation; Neuroprotective microenvironment; Parkinson's disease

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1. Introduction

Parkinson's disease (PD) is a prevalent neurodegenerative disorder, with its main pathological features being the progressive loss of dopaminergic (DA) neurons in the substantia nigra of the midbrain and the depletion of dopamine in the striatum[1]. Current therapeutic strategies for PD, including pharmacological interventions and deep brain stimulation, only alleviate symptoms but fail to halt disease progression; long-term use may even induce motor complications.

Cell replacement therapy has emerged as a promising avenue for the treatment of PD. From the early fetal brain tissue transplantation to the current stem cell technology, the acquisition schemes of dopaminergic neurons have been

continuously optimized[2]. Clinical studies have demonstrated that transplantation of DA precursor cells derived from human embryonic stem cells (hESCs) can improve motor symptoms in PD patients. However, the therapeutic efficacy is severely limited by two critical bottlenecks: the low survival rate of transplanted cells and the neuroinflammatory microenvironment triggered by the host immune response[3].

Neuroinflammation plays a pivotal role in the pathogenesis of PD. In addition to microglial activation, the peripheral immune system is actively involved in the pathological process[4]. Regulatory T cells (Treg cells), as central modulators of immune homeostasis, exhibit abnormal numbers and impaired functions in both the peripheral blood and lesion sites of PD patients. Recent studies have transcended the traditional view of Tregs as mere immunosuppressors, revealing their neuroprotective effects through non-immunological mechanisms such as direct cell-cell contact[5]. Based on this, an innovative strategy of co-transplantation of autologous Treg cells and dopaminergic neurons has emerged. This strategy aims to establish an immune-exempt microenvironment at the transplantation site to enhance cell survival rate[6]. Preclinical studies have confirmed that co-transplantation can effectively suppress immune responses and promote the recovery of motor function, providing a new paradigm for the treatment of PD that integrates cell replacement and immune regulation. This review provides a detailed explanation for relevant scholars of the mechanism and clinical feasibility of using autologous Treg cells to construct a neuroprotective microenvironment for dopaminergic neuron grafts.

2. Biological characteristics of Treg cells and their role in neuroprotection

2.1. Immune Regulatory Function of Treg Cells

Regulatory T cells (Treg cells) are a specialized subset of CD4+T cells, mainly expressing the transcription factor FoxP3, serving as immune tolerance and preventing autoimmune responses. Treg cells exert immunosuppressive effects through multiple mechanisms, including secreting anti-inflammatory cytokines (such as IL-10, TGF-β and IL-35), contact-dependent inhibition through the engagement of CTLA-4 with CD80/CD86 on antigen-presenting cells, attenuating co-stimulatory signaling; and direct cytotoxicity toward hyperactivated immune cells via the granzyme/perforin pathway. In the pathological milieu of PD, the immunomodulatory capacity of Treg cells is particularly significant——it effectively inhibits neuroinflammatory responses and alleviate damage to dopaminergic neurons.

2.2. Neuroprotective Mechanisms of Treg cells

Emerging evidence indicates that Tregs encompass not only immunomodulatory functions but also the ability to exert direct neuroprotective effects via multiple pathways. In PD animal models, Tregs have been consistently shown to safeguard DA neurons against damage induced by neurotoxins such as MPP^+ (1-methyl-4-phenylpyridinium) and 6-OHDA (6-hydroxydopamine)[7], with contact-dependent signaling emerging as a central mediator of this protection.

Central to Treg-mediated neuroprotection is a contact-dependent mechanism, whereby Tregs exert protective effects via direct physical interaction with DA neurons. Huang et al. found that Treg cells express the transmembrane protein CD47, while dopaminergic neurons express the ligand SIRPA of CD47[7]. The interaction between these two proteins can activate the Rac1/Akt signaling pathway within neurons, thereby protecting dopaminergic neurons from MPP+ -induced toxic damage. When the expression of CD47 or SIRPA is inhibited, the neuroprotective effect of Treg cells is significantly weakened, indicating the importance of this contact-dependent mechanism in neuroprotection.

Treg cells alleviate neuroinflammatory responses by inhibiting the excessive activation of microglia. In the PD mouse model, adoptive transfer of Treg cells can significantly reduce the production of pro-inflammatory cytokines (e.g., TNF-α and IL-1β), while concomitantly elevating the levels of anti-inflammatory cytokines and neurotrophic factors[8]. Furthermore, Tregs suppress the infiltration of neutrophils and macrophages into the central nervous system (CNS) via the secretion of anti-inflammatory cytokines such as IL-10, thereby further mitigating neuroinflammation[9].

Beyond their immunomodulatory capacities, Tregs also secrete a repertoire of neurotrophic factors, including brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), which directly promote the

survival, differentiation, and functional maintenance of DA neurons. Notably, studies have demonstrated that BDNF-loaded exosomes derived from human umbilical cord mesenchymal stem cells (BDNF-EXO) potently inhibit 6-OHDA-induced apoptosis and ferroptosis, thereby protecting DA neurons[10]. Analogously, Tregs are hypothesized to confer neurotrophic support via a comparable mechanism.

Tregs contribute to maintaining BBB integrity, which in turn reduces the infiltration of peripheral immune cells into the CNS and mitigates neuroinflammation. Accumulating evidence indicates that in diverse neurological disease models, Tregs enhance BBB integrity through the regulation of endothelial cell function.Collectively, these multifaceted neuroprotective mechanisms position. Tregs as ideal candidates for engineering a neuroprotective microenvironment, offering novel insights to improve the survival and functional integration of DA neuron grafts.

3. The co-transplantation strategy of autologous Treg cells and dopaminergic neurons

3.1. Theoretical Basis of Co-transplantation

The core objective of co-transplanting autologous regulatory T cells and DA neurons is to establish an immune-privileged microenvironment at the transplantation site. Traditional cell transplantation is hindered by two major challenges: host immune rejection and neuroinflammatory responses, which culminate in the massive early death of transplanted cells[6]. As key regulators of immune homeostasis, Tregs are capable of modulating local immune responses through multiple mechanisms, thereby creating a microenvironment permissive for the survival and functional integration of transplanted neurons.

The use of autologous Tregs confers distinct advantages: first, it avoids allogeneic immune rejection; second, it reduces reliance on exogenous immunosuppressants. Studies have demonstrated that Treg cells isolated from patients' peripheral blood and expanded in vitro exhibit significantly higher safety profiles compared to allogeneic cell sources. Moreover, in vitro activation and expansion further enhance the immunosuppressive function and neuroprotective capacity of Tregs.

3.2. Implementation methods of co-transplantation

CD4+CD25+CD127 low Treg cells were isolated from the peripheral blood of patients and expanded in vitro by factors such as anti-CD3 /CD28 antibodies, IL-2 and retinoic acid. Studies have shown that this process can effectively restore the functional defects of Treg cells in PD patients and rebuild their immunosuppressive capacity.

A9-type dopaminergic neuron precursor cells are differentiated from patients' own induced pluripotent stem cells (iPSCs) or human embryonic stem cells (hESCs). Recent advances in 3D differentiation protocols employ combinations of small molecules with fully defined components, enabling large-scale generation of high-purity ventral midbrain dopaminergic precursor cells.

Treg cells and dopaminergic neuron precursor cells are mixed at an optimized ratio and transplanted into the patient's putamen via stereotactic techniques. Preclinical studies have indicated that bilateral putaminal transplantation more comprehensively restores dopaminergic function and requires only short-term immunosuppressive support to achieve long-term immune tolerance.

3.3. Preclinical research evidence

In preclinical PD models, the co-transplantation strategy has exhibited substantial therapeutic efficacy. Park et al.'s research indicates that co-transplantation can significantly increase the survival rate of transplanted cells, inhibit CD8+T cell infiltration and microglial cell activation, and promote the recovery of motor function[6]. The survival rate of dopaminergic neurons in the co-transplantation group was significantly higher than that in the single-transplantation group.

Subsequent studies have confirmed that Treg cells not only enhance the survival rate of transplanted cells but also foster their functional integration into the host neural circuitry. Behavioral tests showed that the animals in the co-

transplantation group improved more significantly in terms of motor coordination and motor speed. At the mechanism level, in addition to immunomodulatory effects, Treg cells also secrete extracellular vesicles to deliver neurotrophic factors and mirnas, supporting neuronal survival and functional maturation.

3.4. Auxiliary strategies for Enhancing Treg Cell Function

Drug intervention is an important supplementary strategy for enhancing the function of Treg cells. Among them, the VIPR2 agonist LBT-3627 demonstrated significant effects in the PD rat model, enhancing the activity of Treg cells without affecting their quantity, while reducing inflammatory microglia and improving the survival of dopaminergic neurons and striatal density. In the α -synuclein overexpression model, LBT-3627 can effectively salvage the functional defects of Treg cells, presenting a dose-dependent protective effect.

Other strategies, including the use of low-dose IL-2, rapamycin and retinoic acid, etc., can all promote the expansion and functional maturation of Treg cells. When these methods are applied in combination with the co-transplantation strategy, they can further optimize the transplantation microenvironment and improve the therapeutic effect.

4. Challenges and Prospects

The co-transplantation strategy of autologous regulatory T cells and DA neurons, as an emerging direction in the treatment of PD, faces multiple technical bottlenecks and safety challenges on its clinical transformation path. Therefore, a thorough analysis of these challenges and exploration of feasible solutions are the keys for this therapy to move from basic research to clinical application.

4.1. Technical Challenges and Solutions

The primary technical hurdle stems from the inherent functional defects of Treg cells in PD patients themselves. Studies have shown that not only may the number of Tregs be reduced in the periphery and brain of PD patients, but their immunosuppressive function is also significantly impaired—characterized by unstable Foxp3 expression and a diminished capacity to inhibit effector T cell activation. Failure to correct this intrinsic functional deficiency will severely compromise the establishment of a neuroprotective microenvironment. To address this, researchers have made substantial progress by optimizing in vitro expansion protocols. Incorporating specific cytokine combinations into the culture system-such as high concentrations of interleukin-2 (IL-2)-promotes Treg survival and proliferation, while transforming growth factor-β (TGF-β) helps sustain their phenotypic stability. Additionally, the use of small-molecule compounds like VIPR2 agonists can specifically enhance Treg inhibitory function, partially mitigate the functional deficits of Tregs from PD patients, and provide a novel approach to obtaining high-quality therapeutic cells .

Cell product purity is another critical factor related to treatment safety. During Treg expansion, contamination with a small fraction of effector T cells may lead to post-transplantation attack on newly engrafted dopaminergic neurons, resulting in treatment failure. Thus, establishing a stringent purification process is paramount. Utilizing flow cytometric sorting based on surface marker combinations (e.g., $CD4^+CD25^+CD127low/-$) enables efficient isolation of high-purity Treg populations and effective exclusion of effector T cell contamination. At the same time, for dopaminergic neuron precursors differentiated from pluripotent stem cells, it is also necessary to ensure their high purity to fundamentally reduce the risk of tumorigenesis that may be caused by the residue of undifferentiated cells.

Determining the optimal cell ratio and transplantation timing is a key parameter governing therapeutic efficacy. Preclinical studies have demonstrated that a suboptimal Treg-to-dopaminergic neuron ratio may result in insufficient or excessive immunosuppression, thereby compromising treatment outcomes. The choice of transplantation timing is even more critical: intervention should be performed in the early stages of the disease. When nigrostriatal degenerative changes are not severe and the neuroinflammatory environment is relatively mild, the survival rate and functional integration efficacy of transplanted cells are optimal. This suggests that future clinical applications should focus on early-stage PD

patients.

4.2. Considerations of Safety and Effectiveness

The clinical translation of this strategy must undergo rigorous safety and efficacy evaluations. Safety concerns primarily focus on tumorigenicity and excessive immunosuppression. Tumorigenic risk is mainly attributed to the persistence of undifferentiated pluripotent stem cells; however, advances in differentiation technologies have shown that transplantation of high-purity dopaminergic neuron precursors can significantly mitigate this risk. The concern over excessive immunosuppression stems from the powerful immunosuppressive function of Treg cells. However, the action of Treg is characterized by antigenic specificity and locality. They mainly accumulate at the transplantation site to exert their effects and have limited impact on the systemic immune system. Long-term follow-up data from preclinical studies showed that there was no significant increase in the incidence of infection or tumors in the treatment group of animals.

A core issue related to the persistence of therapeutic effects is ensuring that Tregs can maintain functional stability for an extended period post-transplantation. The chronic inflammatory microenvironment of PD may compromise Treg phenotypic stability. For this reason, researchers are exploring strategies to enhance Treg functional persistence through genetic engineering, or to provide necessary cytokine support via sustained-release technologies post-transplantation, thereby enabling Tregs to sustain long-term protective effects in the brain microenvironment.

4.3. Future Research Directions

To facilitate the clinical translation of this strategy, future research should focus on the following directions: First, leveraging cutting-edge technologies such as single-cell sequencing and spatial transcriptomics to deeply dissect the molecular mechanisms underlying Treg crosstalk with diverse brain-resident cell types, and fully delineate their neuroprotective networks. Second, develop individualized treatment plans to tailor cell products and transplantation regimens based on patients' immune profiles and genetic backgrounds. Furthermore, explore combination therapy paradigms with neuromodulatory techniques or neurotrophic factors to enhance therapeutic efficacy through multi-target intervention. Finally, through rigorously designed clinical trials——progressing from safety assessment to dose-finding and efficacy validation---steady advancement of clinical translation will be achieved.

5. Conclusion

The establishment of a local immune-tolerant microenvironment for transplanted DA neurons using autologous regulatory T cells represents an innovative therapeutic paradigm that elegantly integrates two major therapeutic strategies: immune regulation and cell replacement. The core advantage of this strategy lies in its multi-dimensional protective mechanism: Tregs establish a robust survival safeguard for vulnerable DA neuron grafts through diverse pathways, including contact-dependent protection, effective suppression of neuroinflammation, and provision of neurotrophic support. This synergistic protective effect substantially enhances the survival rate of transplanted cells, promotes their functional maturation and integration into host neural circuits, thereby laying the groundwork for sustained motor function improvement in PD patients[6].

While refinements are still required regarding the functional stability of cells and standardization of preparation protocols, these challenges will be progressively mitigated with deeper insights into the biological characteristics of Tregs, continuous breakthroughs in biotechnology, and the accumulation of clinical trial data. The co-transplantation strategy of autologous Tregs and DA neurons paves a novel avenue for PD treatment and embodies a novel concept of enhancing cell therapy efficacy by reshaping the local microenvironment. It holds promise as a pivotal breakthrough in the field of PD therapeutics and offers renewed hope to countless patients.

Disclosure statement

The author declares no conflict of interest.

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