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The Technical System, Clinical Application and Future Prospects of Pluripotent Stem Cells (ESC/iPSC) Mediated Nerve Regeneration

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Abstract: This review systematically outlines the technological framework and clinical applications of neural regeneration mediated by pluripotent stem cells (ESCs/iPSCs). The article first compares the fundamental differences between the two: ESCs face ethical controversies regarding their embryonic origin and challenges related to immune rejection; while iPSCs support autologous transplantation, their reprogramming process may lead to genomic abnormalities, and the presence of residual undifferentiated cells poses a tumorigenic risk. The article traces the trend of directed differentiation technologies evolving from two-dimensional culture to three-dimensional organoids and details their practical applications in diseases such as stroke, Alzheimer's disease, and spinal cord injury—particularly in spinal cord injury models, where transplanted cells have achieved long-distance axonal regeneration and circuit reconstruction. Addressing core bottlenecks currently facing the field—such as low differentiation efficiency, difficulties in functional integration, and tumorigenicity—this paper explores breakthrough pathways through cutting-edge technologies including gene editing, organoids, and AI-enabled approaches. Finally, it compares the clinical advantages and disadvantages of ESCs and iPSCs, noting that while challenges remain, the deep integration of interdisciplinary technologies is accelerating the translation of stem cell therapies into standard clinical treatments, bringing revolutionary hope to patients with neurological diseases.

Keywords: Pluripotent Stem Cells; Neural Regeneration; Clinical Application; Spinal Cord Injury.

1. Introduction

1.1. Overview of Core Technology Types of Pluripotent Stem Cells

The core definition of pluripotent stem cells is characterized by self-renewal ability and the potential to differentiate into three germ layer-derived cell types. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are the two main forms. ESCs are derived from the inner cell mass of blastocyst-stage embryos, while iPSCs are obtained through somatic cell reprogramming. Research shows that specific chemical small molecule combinations can effectively induce human somatic cells to enter a pluripotent state, and this non-integration method reduces the potential risks caused by the random insertion of exogenous genes[1]. Although ESCs and iPSCs are both pluripotent, there is an essential difference in their clinical path. ESCs face ethical restrictions derived from embryo acquisition and immune rejection of allogeneic transplantation. In contrast, iPSCs support autologous transplantation, which theoretically can minimize immune rejection, but their clinical application is limited by genomic abnormalities that may occur during the reprogramming process and the tumorigenic risk posed by undifferentiated cell residues.

1.2. Clinical Needs and Scientific Value of Nerve Regeneration

Central nervous system injuries and neurodegenerative diseases, such as Alzheimer's disease (AD), spinal cord injury (SCI) and ischemic stroke, are the main factors leading to high disability and mortality rates worldwide. Most existing treatment methods are symptomatic and cannot achieve neural structure repair and functional reconstruction. Stem cell therapy provides a new paradigm for nerve regeneration through cell replacement and paracrine effects. Recent clinical research data confirm the potential of this strategy. In spinal cord injury models, transplanted iPSC-derived cells can differentiate into neurons and glial cells, forming neural circuits that bridge the injury area. New axons can extend ultra-long distances, establish functional synapses with distal host neurons, and ultimately achieve significant motor function recovery in animal models. In non-human primate SCI models, after transplantation of clinicalgrade H9-scNSCs (spinal cord-oriented differentiated neural stem cells), hundreds of thousands of axons (up to 139,900) extended 39 mm through the injury area, and the recovery rate of fine hand motor function reached 53.4% (only 5.8% in the control group), fully confirming the synergy between rehabilitation training and cell therapy (R^2=0.77) [2]. Together, this evidence shows that iPSC-based neuroregeneration strategies have clear clinical translation value.

2. The Key Technical System of Directional Differentiation of Pluripotent Stem Cells into Neurons

2.1. Molecular Mechanism Basis of Directional Differentiation

ESCs/iPSCs are directed toward the neural lineage through the coordination of internal transcription programs and external signaling pathways. Core transcription factors, such as neurogenin 2 (NGN2) and achaete-scute homolog 1 (ASCL1), play a leading role in initiating the neural differentiation process[1]. In addition, epigenetic regulatory mechanisms are crucial for precise cell fate decisions. Histone

modification and DNA methylation dynamically regulate chromatin accessibility, thus finely guiding ESCs/iPSCs to differentiate into specific neuronal subtypes.

2.2. Practical Process and Key Parameters of in Vitro Differentiation

Standard in vitro neural differentiation follows a staged protocol that simulates in vivo neurodevelopment through the sequential addition of small molecule compounds and growth factors. Authoritative research has provided a large-scale generation protocol for functional human iPSC-derived neurons, characterized by high reproducibility and yield. Current technology is evolving from two-dimensional (2D) monolayer culture to three-dimensional (3D) organoid culture systems. 3D organoids better recapitulate the cellular diversity and spatial tissue architecture of the human brain. For example, in Parkinson's disease (PD) research, iPSC-derived 3D organoid models can accurately simulate the microenvironment of midbrain dopaminergic neurons, providing an ideal platform for improving differentiation efficiency and functional maturity [3]. In this system, the use of chemically defined serum-free media and the introduction of glial cell co-culture in the late differentiation stage have been confirmed to significantly promote synaptic maturation and network activity of iPSC-derived neurons.

2.3. Differentiation Efficiency and Function Verification Method

Functional verification of ESC/iPSC-derived neurons is a critical step in evaluating differentiation success. Molecular phenotypic identification detects the expression of neuronal markers (such as βIII-tubulin, MAP2) through immunocytochemistry. Functional characterization uses patch-clamp technology to record action potentials and postsynaptic currents, or calcium imaging to observe spontaneous synchronous activity of neuronal clusters. Differentiation efficiency and heterogeneity analysis apply single-cell RNA sequencing technology to unbiasedly analyze the cellular composition of differentiated populations. In preclinical verification of autologous iPSC-derived midbrain dopaminergic progenitor cells (iPSC-mDAC) for PD patients, Harvard Medical School confirmed the purity and activity of differentiated cells using this technology combined with functional assays[3]. The published ESC/iPSC neurodifferentiation single-cell atlas provides a high-resolution reference standard for this purpose. Single-cell multi-omics technology further reveals that during the integration of iPSC-derived neurons into neural circuits, their gene regulatory networks undergo dynamic evolution: early networks primarily regulate cell morphogenesis, while late networks dominate synaptic organization and plasticity.

3. Application Practice of Pluripotent Stem Cells Inneuroregeneration-related Diseases

3.1. Ischemic Stroke

After stroke, neurons in the core infarct area undergo irreversible death, and the local microenvironment severely inhibits regeneration. iPSC-based strategies are diverse. Among them, iPSC-derived extracellular vesicles have attracted attention as a cell-free treatment option. A study by a joint team from USC and the University of Zurich shows that these vesicles can deliver neurotrophic factors and regulatory miRNAs, effectively modulating post-stroke immune inflammatory responses and promoting angiogenesis. The survival rate of transplanted cells reached 78%, and they differentiated into functional GABAergic and glutamatergic neurons, restoring gait coordination and spontaneous motor function in stroke mice to 92% of pre-operative levels. The team also established a GMP-compliant serum-free culture system, and its phase I clinical trial was approved by the FDA and launched in 2024[1], providing key technical support for clinical translation.

3.2. Alzheimer's Disease

In AD research, the core application of iPSC technology is disease modeling. Somatic cells from patients carrying AD pathogenic mutations are reprogrammed into iPSCs and then differentiated into neurons and glial cells, which can reproduce key pathological features such as Aβ accumulation and Tau hyperphosphorylation in vitro. Using iPSC-constructed 3D brain organoid models, the multilayer structure and neuroinflammatory environment of the cerebral cortex can be more realistically simulated. This technical approach is consistent with the application logic of 3D organoids in PD research, providing a highly biomimetic platform for disease mechanism analysis and drug screening[1].

3.3. Spinal Cord Injury

The goal of spinal cord injury repair is to achieve axon regeneration and neural circuit reconstruction. Studies have revealed the cellular and molecular mechanisms by which transplanted iPSC-derived stem cells promote functional axon growth across complete injury sites, confirming that new axons can form effective neural relays to bridge damaged upstream and downstream pathways. This breakthrough in basic research has laid the foundation for clinical translation. For the first time, a phase I/IIa clinical trial confirmed the safety and preliminary efficacy of transplanting human iPSC-derived neural progenitor cells for the treatment of spinal cord injury[2]. The iPSC-derived spinal neural progenitor cells (spNPCs, XS228 injection) developed by the research team achieved significant sensory and motor function recovery in SCI animal models through a dual mechanism of "cell replenishment (differentiation into motor neurons/V2 interneurons) + environmental modulation (inhibition of inflammation and glial scar formation)". Currently, the world's first human transplantation has been completed, with initial positive therapeutic effects.

4. Technical Bottlenecks and Innovative Breakthroughs Instem Cell Nerve Regeneration

4.1. Core Technical Bottlenecks

The main challenges currently facing the field include: in vitro differentiation bottlenecks, where ESC/iPSC-derived neurons often exhibit low survival rates and insufficient functional maturity, with electrophysiological characteristics and synaptic network activity resembling early developmental stages. Heterogeneity of the final differentiation product is also a common problem. Clinical translation barriers include immune rejection faced by ESC transplantation; tumorigenic potential in iPSCs; and low engraftment efficiency and difficulty in functional integration

of transplanted cells in the host lesion microenvironment.

4.2. Innovative Breakthrough Path

In response to these bottlenecks, cutting-edge technological approaches provide solutions: Gene editing technology can use the CRISPR-Cas9 system to precisely modify iPSCs. For example, the team from the Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, analyzed the structural and functional integration mechanism of transplanted cells with host neural circuits through CRISPR gene editing and rabies virus tracing in a hypoxic-ischemic encephalopathy (HIE) model, confirming that human ESCderived striatal neural progenitor cells (SNPs) can accurately reconstruct the basal ganglia pathway[4]. In addition, knocking out immunogenicity-related genes to create universal cell lines has also become an important direction. Organoid technology can provide in vitro models that more closely approximate physiological states. Studies confirm that transplanted iPSC-derived organoids can continue to develop in the host brain and establish functional connections with the host neural network. Small molecule induction strategies can efficiently guide the targeted differentiation of iPSCs into desired neural cell types in a non-genetic and cost-effective manner.

5. The Integration of New Technologies Empowers Stem Cellnerve Regeneration

5.1. Single-cell multi-omic Technology

The revolution of single-cell multi-omic techniques (such as scRNA-seq and scATAC-seq) lies in their ability to analyze cellular heterogeneity during iPSC differentiation at single-cell resolution. By simultaneously analyzing the transcriptome and chromatin accessibility of individual cells, differentiation trajectories can be accurately mapped and rare cell subtypes identified. This technology has been applied to iPSC neurodevelopment research, successfully constructing gene regulatory networks that govern synaptic development and identifying key transcription factors. In preclinical PD studies, single-cell multi-omic technology was used to evaluate the differentiation uniformity and functional stability of iPSC-mDACs, providing data support for the establishment of a personalized efficacy prediction system[3].

5.2. AI and Machine Learning Applications

Artificial intelligence (AI) is deeply empowering multiple links in this field. Researchers have developed AI-driven models that can predict the neural differentiation efficiency of iPSCs by analyzing initial molecular characteristics, providing a data-driven tool for optimizing differentiation protocols and screening key small molecules. This technology has shown potential in preclinical verification of PD cell therapy, enabling rapid screening of iPSC clones with high differentiation efficiency and reducing clinical translation risks[3].

6. Discussion

6.1. Comparison of Advantages and Disadvantages of ESC and iPSC Inneuroregeneration Applications

Due to their patient-specific origin, iPSCs can theoretically minimize immune rejection from allogeneic transplantation, giving them a significant advantage in personalized medicine. Their production process does not involve embryos, resulting in fewer ethical controversies. The Kyoto University team used HLA-typed hiPSC-derived CORIN+ dopaminergic progenitor cells to treat PD patients. The high-dose group showed a 44.7% increase in dopamine uptake, with 5 patients experiencing improved motor symptoms. Immunosuppressants were discontinued 15 months after surgery without rejection, confirming the safety and dosedependent efficacy of this approach[5]. In recent years, "universal" cell banks based on iPSCs from healthy donors have made progress in clinical translation. In contrast, ethical constraints and immune matching issues remain major obstacles to the clinical application of ESCs. Although the Memorial Sloan Kettering Cancer Center team used hESC-derived dopamine progenitor cells to treat PD patients, resulting in a 35% improvement in the high-dose group's MDS-UPDRS III OFF score with no serious complications for 1 year post-surgery[1], the development of low-immunogenic ESC systems through gene editing technology remains an active research direction.

6.2. Challenges and Feasibility of Clinical Transformation of New Technologies

Cutting-edge technologies such as iPSC-derived organoids and gene editing are moving from the laboratory to clinical practice, facing complex translation barriers. The first challenge is establishing strict current Good Manufacturing Practice (cGMP) standardized production processes to ensure high uniformity and stability of each batch of products. For example, the joint USC and University of Zurich team established a GMP-compliant culture system for iPSCNPCs for stroke treatment[1]. Secondly, thorough tumorigenicity evaluation and long-term safety monitoring must be conducted. In preclinical PD studies, Harvard Medical School verified the tumorigenicity and toxicity of iPSC-mDACs through a 39-week GLP mouse model[3]. In a phase I/IIa clinical trial for PD, teams from Korea University and Yonsei University followed 12 moderate to severe patients for 12 months with no serious adverse events, initially addressing the three core issues of "safety, efficacy, and production feasibility" [3].

7. Conclusion

This review systematically summarizes the technological framework and clinical applications of pluripotent stem cell-mediated neural regeneration, comparing the unique advantages and limitations of ESCs and iPSCs. Current research has demonstrated the therapeutic potential of stem cell therapy in stroke, Alzheimer's disease, and spinal cord injury, with significant progress in directed differentiation and functional integration. However, challenges such as low differentiation efficiency, tumorigenic risk, and clinical standardization remain. Future development will rely on the deep integration of interdisciplinary technologies including gene editing, organoids, and artificial intelligence. Continued technological innovation and rigorous clinical trials will accelerate the translation of stem cell therapies into standard clinical treatments, bringing revolutionary hope to patients with neurological disorders.

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