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Research progress and challenges of stem cell therapy for Parkinson's disease

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Abstract. Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to striatal dopamine depletion and resulting motor (e.g., tremor, bradykinesia) and non-motor symptoms (e.g., cognitive decline and sleep abnormalities). Current treatment strategies mainly focus on dopamine replacement therapy and deep brain stimulation. Although these methods can temporarily relieve symptoms, they cannot reverse nerve damage, and long-term use is associated with obvious side effects and potential risks. There is thus an urgent clinical need for new radical treatment methods. Stem cell therapy, leveraging self-renewal, multi-directional differentiation and paracrine regulation, has become a research hotspot in the field of PD treatment, bringing new hope for the radical cure of PD. This review synthesizes the research status and core issues of stem cell therapy for PD, offering practical insights for future research and clinical trials, and promoting the standardization and interdisciplinary development of regenerative neuroscience.

Keywords: Parkinson's disease, stem cell therapy, mesenchymal stem cells

1. Introduction

Parkinson's disease ranks as the second most prevalent neurodegenerative disorder worldwide, predominantly affecting middle-aged and elderly populations, with disease risk rising sharply with age. Epidemiological statistics reveal that the prevalence of PD among people over 65 is approximately 1.7%, with nearly 100,000 new cases diagnosed annually [1]. The core pathological lesion of PD lies in the progressive apoptosis of dopaminergic neurons within the substantia nigra pars compacta, accompanied by abnormal aggregation of α-synuclein to form Lewy bodies. This results in insufficient dopamine secretion in the striatum and subsequently triggers a wide range of motor and non-motor manifestations [2]. Driven by rapid advances in regenerative medicine, stem cell therapy has delivered novel strategies for achieving curative effects against PD. Multiple stem cell varieties including embryonic stem cells, induced pluripotent stem cells and mesenchymal stem cells have been widely adopted in PD therapeutic research, and relevant basic experiments and early-stage clinical trials have validated their moderate safety and therapeutic efficacy [3].

Nevertheless, numerous research gaps persist within this field. The exact molecular mechanisms underlying stem cell-based PD therapy remain incompletely elucidated, especially the regulatory pathways governing paracrine activity. Transplanted stem cells exhibit low survival rates inside the brain and weak

integration with the host neural circuits, which undermines long-term therapeutic outcomes. No standardized manufacturing workflow for stem cell preparation has been formulated, and uniform criteria for cell isolation, in vitro culture and directed differentiation are still absent. Concerns over long-term safety, tumorigenic risks and immune rejection following allogeneic transplantation hinder the clinical translation of stem cell therapeutics [4]. Accordingly, this paper centers on mesenchymal stem cell therapy, systematically reviewing its biological merits, latest research progress, prevailing obstacles and prospective developmental directions for treating Parkinson's disease.

2. Pathogenesis of Parkinson's disease and clinical treatment demands

2.1. Pathological mechanisms

The hallmark pathological features of Parkinson's disease are the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the formation of Lewy bodies from misfolded, aggregated α-synuclein [5]. These neurons project nerve fibers to the striatum to regulate movement, mood and cognitive functions. Massive neuronal loss drastically reduces striatal dopamine concentrations, giving rise to classic motor symptoms such as resting tremor, bradykinesia and myotonia [6].

PD pathogenesis arises from the combined effects of genetic variants, environmental toxicants and impaired intracellular homeostasis. From a genetic perspective, variants of SNCA, LRRK2, Parkin and DJ-1 genes are strongly linked to familial PD. SNCA mutations facilitate the assembly of toxic oligomers that constitute the primary structural component of Lewy bodies [7]. Parkin deficiency impairs mitochondrial autophagy, causing accumulation of damaged mitochondria and elevated oxidative stress that accelerates neuronal degeneration [8].

In terms of environmental triggers, neurotoxicants including MPTP, rotenone and paraquat can cross the blood-brain barrier, inhibit mitochondrial respiratory chain activity and directly induce dopaminergic neuron apoptosis [9]. Additionally, oxidative stress, neuroinflammation, mitochondrial dysfunction and synaptic malfunction interact synergistically to drive neuronal degeneration throughout the entire progression of PD [10].

2.2. Theoretical foundation of stem cell therapy

Stem cells possess inherent self-renewal capacity and multi-lineage differentiation potential, enabling them to mature into functional dopaminergic neurons under defined culture conditions [11]. Given that the root pathological defect of PD is the depletion of dopaminergic neurons, the core logic of stem cell therapy is as follows: transplanted stem cells differentiate to replace damaged neurons, replenish striatal dopamine supplies and restore the normal function of neural circuits.

Furthermore, stem cells secrete bioactive mediators such as nerve growth factor and vascular endothelial growth factor via paracrine signaling. These bioactive molecules exert neuroprotective and anti-inflammatory functions, facilitate endogenous neural repair and inhibit dopaminergic neuronal apoptosis [12]. This therapeutic strategy can not only arrest disease progression but also achieve disease-modifying effects by slowing or reversing pathological changes, overcoming the drawbacks of traditional symptomatic interventions.

2.3. Underlying therapeutic mechanisms of stem cells against Parkinson's disease

Four primary mechanisms account for the therapeutic effects of stem cell transplantation in PD:

Cell replacement: After directional induction, stem cells mature into functional dopaminergic neurons that replenish lost neurons in the substantia nigra, reconstruct the nigrostriatal neural circuit and restore dopamine secretion [13]. In animal models, transplanted mesenchymal stem cells develop into Tyrosine Hydroxylase (TH)-positive cells, confirming their neuronal differentiation capability [14].

Neuroprotection: Stem cells release neurotrophic factors including Nerve Growth Factor (NGF) and Glial Cell Line-Derived Neurotrophic Factor (GDNF) through paracrine pathways. These molecules block dopaminergic neuron apoptosis, reduce abnormal α-synuclein aggregation and alleviate neurotoxic damage [15].

Immunomodulation: PD brains display severe neuroinflammation triggered by activated microglia and elevated pro-inflammatory cytokines such as TNF and IL-1β [16]. Stem cells restrain microglial activation, downregulate pro-inflammatory mediators and boost anti-inflammatory cytokine production to remodel the brain's immune microenvironment [17].

Metabolic and mitochondrial support: Stem cells transfer intact mitochondria to injured neurons to restore respiratory chain function, lower reactive oxygen species levels and mitigate oxidative stress. They also regulate autophagic pathways to eliminate misfolded proteins and damaged organelles, thereby maintaining stable neuronal homeostasis [18].

3. Major stem cell categories and their therapeutic applications

3.1. Induced Pluripotent Stem Cells (iPSCs)

Induced Pluripotent Stem Cells (iPSCs) are pluripotent cell lines generated by reprogramming human somatic cells (e.g., skin fibroblasts, blood cells) via introduction of transcription factors Oct4, Sox2, Klf4 and c-Myc. Their differentiation potential closely resembles that of embryonic stem cells, and they can be efficiently differentiated into functional dopaminergic neurons, rendering them a primary cell source for PD cell replacement therapy [19].

Advantages: They raise no ethical concerns as embryo destruction is unnecessary; patient-derived autologous iPSCs eliminate immune rejection and support personalized treatment regimens [20]; robust proliferation and directed differentiation capacity allow mass production of clinical-grade cell preparations.

Limitations: Drawbacks include low reprogramming efficiency, complex differentiation protocols and high culture expenses. In addition, viral vector-based reprogramming poses risks of insertional mutagenesis and tumorigenesis, and the purity and functional stability of differentiated neurons still need further improvement [21].

Preclinical studies verify that transplantation of iPSC-derived dopaminergic neurons alleviates bradykinesia and balance impairment in MPTP-lesioned PD mice, raises striatal dopamine levels and mitigates substantia nigra neuron loss [22]. CRISPR/Cas9 gene editing technology can correct pathogenic mutations such as SNCA or LRRK2 prior to differentiation and transplantation to further enhance therapeutic efficacy [23]. Multiple clinical trials are currently underway, with preliminary data demonstrating favorable safety profiles and no severe adverse events following autologous iPSC-derived dopaminergic neuron transplantation [24].

3.2. Mesenchymal Stem Cells (MSCs)

Mesenchymal Stem Cells (MSCs) are mesoderm-derived adult stem cells widely harvested from bone marrow, adipose tissue, umbilical cord blood and placental tissue. They feature convenient sampling, potent in vitro

expansion and low immunogenicity with mild rejection after allogeneic transplantation, rendering them the most commonly utilized cell type for PD stem cell therapy to date [25].

Advantages: MSCs can be obtained through minimally invasive procedures including bone marrow aspiration and liposuction; simple culture protocols enable rapid expansion to clinically required cell dosages; HLA matching is not mandatory, ensuring high safety for allogeneic transplants. Beyond limited differentiation into dopaminergic neurons, their therapeutic effect mainly relies on paracrine secretion of neurotrophic factors to mediate neuroprotection and immune regulation [26].

Disadvantages: MSCs possess relatively restricted differentiation potential, with low efficiency of directed differentiation into dopaminergic neurons, and the resulting neurons exhibit inferior functional stability compared to embryonic stem cells and iPSCs. Transplanted MSCs show low survival rates in the brain, limiting long-term therapeutic persistence [27].

Abundant preclinical evidence verifies that MSC grafting ameliorates motor dysfunction in PD animal models. Implantation of bone marrow MSCs into 6-OHDA-lesioned rats reduces rotational behavior and enhances motor coordination [28]. Intranasal and intramuscular delivery of adipose-derived MSCs continuously relieves motor and non-motor symptoms while lowering cerebral inflammatory levels in PD model animals [29].

In clinical trials, Venkataramana et al. unilaterally infused autologous MSCs into seven PD patients, with follow-up durations ranging from 10 to 36 months. Three subjects exhibited decreased Unified Parkinson's Disease Rating Scale (UPDRS) scores and lower Hoehn-Yahr staging, accompanied by obvious improvements in facial expression and gait without severe adverse reactions [30]. Carstens et al. administered autologous adipose MSCs via intranasal and intramuscular routes and similarly observed alleviated motor and non-motor symptoms, reduced levodopa equivalent doses and improved quality of life [31]. Phase I/II clinical trials of MSC therapy for PD have been initiated across multiple countries to primarily evaluate safety and therapeutic efficacy [32].

3.3. Neural Stem Cells (NSCs)

Neural Stem Cells (NSCs) are adult stem cells residing in brain regions including the hippocampus and subventricular zone, endowed with self-renewal capacity and the ability to differentiate into neurons, astrocytes and oligodendrocytes. Under directional induction, they mature into functional dopaminergic neurons, marking them as a promising candidate for PD cell replacement therapy.

Their core advantages lie in neural-compatible developmental differentiation cascades, robust capacity to integrate into host neural circuits, and relatively low immunogenicity for tissue-matched grafts. NSCs also secrete neurotrophic factors through paracrine signaling to boost endogenous neural repair [33]. However, NSCs face severe limitations in sourcing. Fetal brain-derived NSCs trigger ethical controversies, while adult brain tissue contains scarce NSCs that are difficult to isolate and amplify in vitro. Their weak proliferative potential impedes large-scale generation of clinical-grade cellular products and limits their wide clinical adoption.

Preclinical experiments indicate that transplanted NSCs differentiate into dopaminergic neurons to replenish striatal dopamine secretion and ameliorate motor dysfunction in PD animal models [34]. Meanwhile, NSCs promote survival and self-repair of endogenous dopaminergic neurons in host tissue to amplify therapeutic benefits. Current NSC research for PD remains predominantly at the preclinical stage, with a small number of early-phase clinical trials preliminarily confirming safety. Nonetheless, barriers in cell acquisition and expansion hinder widespread clinical translation [35].

3.4. Comparative summary of clinical application progress for three stem cell types

Induced pluripotent stem cells, mesenchymal stem cells and neural stem cells differ drastically in their positioning and developmental progress for PD treatment.

Mesenchymal stem cells exhibit the most mature translational progress, owing to accessible tissue harvesting, straightforward culture protocols, low allogeneic immune rejection risks and absent ethical controversies. Sufficient animal experimental data and multiple global Phase I/II clinical trials make MSCs the mainstream choice for PD stem cell therapy at present. Still, their low efficiency of differentiation into dopaminergic neurons and short in vivo survival duration restrict sustained long-term efficacy.

Induced pluripotent stem cells completely eliminate ethical issues associated with embryonic stem cells and support personalized autologous treatment with outstanding differentiation potential. Combined with gene editing tools, they deliver exceptional therapeutic prospects, and existing clinical trials have verified their safety. However, technical bottlenecks such as low reprogramming efficiency, high cultivation costs and latent tumorigenic risks require continuous optimization, preventing large-scale popularization for the time being.

Neural stem cells display strong neural specificity, high lineage matching and optimal integration with host neural circuits, enabling precise paracrine-mediated repair. Yet constrained by scarce sources, difficult isolation and expansion, plus ethical disputes over partial tissue origins, most related research remains confined to preclinical animal studies with only a handful of preliminary clinical explorations, marking the slowest overall application pace.

In summary, the three cell types complement and advance one another: MSCs support near-term clinical investigations, iPSCs represent the future direction of personalized curative therapy, and NSCs facilitate in-depth research on neural circuit repair mechanisms. All three cell types face identical translational barriers: poor intracerebral cell viability, incomplete directed differentiation and unresolved long-term safety hazards, which call for systematic technical breakthroughs.

4. Future outlook and developmental trends

4.1. Advances in clinical trials

Continuous optimization of stem cell technology and deepening research have steadily pushed forward clinical trials of stem cell therapy for PD. Future research priorities will center on systematic evaluation of safety and efficacy, alongside standardization of therapeutic regimens. At present, numerous Phase I/II clinical trials utilizing embryonic stem cells, iPSCs and MSCs have been launched worldwide, primarily aiming to validate the safety of stem cells from diverse sources and various transplantation protocols while conducting preliminary efficacy assessments [36]. For instance, China, India and other nations have initiated Phase I/II clinical trials of MSC therapy for PD, focusing on monitoring post-transplant adverse reactions and fluctuations in indicators such as UPDRS scores and dopamine concentrations [37].

In the subsequent stage, existing clinical trials will enroll larger cohorts and prolong follow-up durations to confirm the long-term safety and sustained therapeutic effects of stem cell-based cellular products. Simultaneously, transplantation parameters including cell dosage, delivery routes and intervention timing will be optimized to raise transplanted cell survival and integration efficiency for enhanced therapeutic outcomes [38]. Furthermore, multi-center clinical trials will be given priority to strengthen cross-institutional cooperation, harmonize unified trial criteria, establish standardized clinical management guidelines and pave the way for the broad clinical translation of stem cell interventions against PD.

4.2. Directions of integrated technology development

The combination of stem cell technology and other frontier biomedical disciplines will become a core developmental trend for PD stem cell interventions, which is expected to overcome current technical hurdles and improve overall therapeutic potency. Among all integrated strategies, the combination of stem cell transplantation and gene therapy holds the greatest translational potential. Gene editing tools such as CRISPR/Cas9 enable genetic modification of stem cells to boost their directed differentiation efficiency into dopaminergic neurons, amplify paracrine activity and mitigate tumorigenic hazards. Moreover, genes encoding neurotrophic and anti-inflammatory factors can be integrated into stem cell genomes to sustain continuous secretion of therapeutic mediators and deliver long-lasting neuroprotection. For example, transduction of MSCs with the GDNF gene markedly enhances their neuroprotective capacity and improves therapeutic outcomes in PD animal models.

Synergy between gene editing technology and iPSCs opens novel avenues for personalized PD treatment. Pathogenic PD-related mutations in iPSCs can be corrected via gene editing before differentiation into dopaminergic neurons for autologous transplantation. This strategy avoids immune rejection while eliminating the detrimental impacts of pathogenic genes to strengthen therapeutic effects. For example, neurons differentiated from LRRK2 G2019S mutation-corrected iPSCs recover normal axonal and dendritic length with restored neuronal functionality.

Furthermore, integration of stem cell technology with nanotechnology and tissue engineering will be progressively advanced. Nanomaterials can be fabricated as stem cell carriers to improve cell survival and targeting precision, enabling accurate colonization of stem cells within the substantia nigra pars compacta and reducing cell loss. Tissue engineering technology enables the fabrication of stem cell-biomaterial composite scaffolds that recapitulate the native cerebral microenvironment, supporting grafted cell survival, directed differentiation and host integration to augment therapeutic benefits. Meanwhile, cell-free therapeutics (e.g., MSC-derived extracellular vesicles) will become a prominent research hotspot as an alternative treatment modality. They exert comparable therapeutic effects to intact MSCs without tumorigenic and immune rejection risks, with the potential to overcome several drawbacks of whole-cell stem cell transplantation.

5. Conclusion

As a prevalent progressive neurodegenerative disease, Parkinson's disease is defined by the progressive degeneration and apoptosis of dopaminergic neurons in the substantia nigra pars compacta. Current clinical interventions merely alleviate symptoms rather than achieve a radical cure. Stem cell therapy stands out as a leading research frontier for PD treatment owing to its unique advantages of cell replacement, neuroprotection and immune modulation, bringing new hope for permanent disease remission. Based on a comprehensive literature review, this paper systematically sorts out research progress of stem cell therapy for PD, analyzes PD pathogenesis and unmet clinical treatment needs, discusses the characteristics, application progress and therapeutic mechanisms of induced pluripotent stem cells, mesenchymal stem cells and neural stem cells, summarizes core challenges facing this field, and forecasts prospective developmental trends.

Existing research demonstrates that all three stem cell varieties possess therapeutic potential against PD yet carry distinct strengths and weaknesses. Induced pluripotent stem cells resolve ethical conflicts and support personalized treatment but suffer from low reprogramming efficiency and high production costs. Mesenchymal stem cells feature convenient sourcing and low immunogenicity as the most widely applied cell type to date, albeit with limited differentiation efficiency. Neural stem cells follow clear neural differentiation pathways and exhibit excellent compatibility with host neural circuits, yet their clinical translation is hindered

by scarce tissue sources and weak proliferative capacity. The core therapeutic mechanisms of stem cell interventions against PD include cell replacement, neuroprotection, immunomodulation and metabolic regulation. These pathways work synergistically to generate prominent therapeutic benefits in preclinical models, recovering motor performance and increasing striatal dopamine concentrations. Early clinical trials have preliminarily confirmed safety, yet multiple obstacles including safety hazards, absence of standardized technical protocols, low transplanted cell survival, high treatment costs and ethical controversies restrict broad clinical translation.

This paper systematically consolidates the research landscape and core bottlenecks of stem cell therapy for PD to provide theoretical references and practical guidance for subsequent investigations. Nevertheless, this study has certain limitations: it may omit recently published clinical trial literature, lacks original experimental verification, and the discussion of stem cell therapeutic mechanisms and clinical translation strategies requires further refinement.

Future research should prioritize five key directions: first, optimize stem cell preparation workflows and establish standardized production systems to upgrade cell quality and differentiation efficiency while cutting manufacturing costs; second, deeply dissect the precise molecular mechanisms of stem cell therapeutic action to supply theoretical support for efficacy enhancement; third, advance clinical trials by expanding sample cohorts, prolonging follow-up durations, refining transplantation protocols and establishing standardized clinical guidelines; fourth, promote cross-disciplinary integration between stem cell technology and frontier tools such as gene editing and nanotechnology to break through existing technical barriers; fifth, resolve ethical disputes, strengthen public science outreach and raise social acceptance of stem cell therapeutics. Simultaneously, cross-disciplinary cooperation should be further strengthened to integrate multiple technical resources and drive in-depth research exploration. Ultimately, these joint efforts aim to achieve disease-modifying curative effects for PD in the near term and deliver long-term clinical benefits to global PD patients..

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