Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.34772

Mesenchymal Stem Cells as an Aging Delay Tool: Implications for Alzheimer's and Parkinson's Disease

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Abstract. The global aging population has driven a steady rise in neurodegenerative diseases like Alzheimer's and Parkinson's, which impose heavy economic, mental, and nursing burdens. Current clinical treatments only offer short-term symptom relief without halting neuronal loss or pathological protein deposition. Mesenchymal stem cells (MSCs) show promise due to their differentiation potential, immunomodulation, paracrine effects, and tissue repair capabilities. This review systematically explores the biological mechanisms of aging, summarizes MSCs' multi-dimensional anti-aging effects, and details their therapeutic pathways and clinical research progress in Alzheimer's and Parkinson's diseases. It also analyzes obstacles to clinical translation, including inconsistent efficacy, long-term safety concerns, and a lack of standardized quality control. The study concludes that MSCs exert neuroprotection mainly by inhibiting chronic inflammation, regulating immune balance, promoting neural regeneration, and releasing paracrine signals. Future research should focus on exosome-based therapies, gene modification, quality control systems, and large-scale clinical trials to advance MSC applications in aging and neurodegenerative disease treatment.

Keywords: Mesenchymal stem cells, Aging, Cellular senescence, Alzheimer's disease, Parkinson's disease, Neuroprotection, Regenerative medicine

1. Introduction

The accelerated aging of the global population structure has gradually evolved into an important social public health problem that restricts long-term socioeconomic stable development and national health construction [1]. As human age increases continuously, the metabolic function of body tissues and organs declines progressively, antioxidant capacity weakens gradually, DNA damage accumulates continuously, and the onset probability of various chronic degenerative diseases rises significantly year by year [2]. Neurodegenerative diseases closely linked to natural aging are typical irreversible chronic lesions, among which AD and PD are the most common clinical types. Such diseases are characterized by progressive massive loss of central neurons, abnormal misfolding and aggregation of specific pathological proteins, persistent low-grade neuroinflammation, and destruction of neural synaptic structure, which eventually lead to severe cognitive dysfunction, memory decline, or abnormal motor disorder and seriously reduce the quality of life of the elderly [3]. Up to now, there is still no effective radical clinical treatment scheme that can completely

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reverse the whole pathological development process of such diseases. Traditional symptomatic drug treatment can only improve clinical manifestations temporarily, and cannot prevent continuous neuronal damage and degenerative progression, resulting in an unsatisfactory long-term clinical curative effect [4]. Therefore, exploring safe, efficient, stable and sustainable new treatment methods for aging-related neurodegenerative diseases has extremely important practical clinical value and profound basic theoretical research significance.

In recent decades, molecular aging mechanisms and stem cell regenerative therapy have become hot and frontier research directions in life medicine. López-Otín and other authoritative scholars systematically summarized nine core characteristic markers of organism aging, including telomere wear, mitochondrial metabolic disorder, epigenetic variation and chronic inflammatory aging, which laid a complete and rigorous theoretical foundation for subsequent research on aging mechanisms and aging-related diseases [2]. Campisi & DiGirolamo deeply clarified the molecular mechanism of stress-induced cellular senescence, and confirmed that persistent accumulation of senescent cells is the key inducement leading to systemic aging and the occurrence of various degenerative diseases [5]. With the rapid iterative development of regenerative medical technology, MSCs have attracted extensive attention worldwide because of their wide and accessible sources, simple isolation and in vitro culture operation, low immune rejection risk, excellent multi-directional differentiation potential and widespread tissue homing ability [6]. A great number of basic animal experiments and preliminary clinical studies have fully verified that MSCs can effectively slow down cellular replicative senescence, reduce oxidative stress damage, inhibit systemic chronic inflammatory reactions, promote damaged nerve tissue repair and endogenous neural regeneration, and show extremely broad application prospects in systemic aging intervention and neurodegenerative disease treatment [7].

This paper adopts a systematic literature review method to sort out multi-path anti-aging biological mechanisms of MSCs, focusing on detailed therapeutic molecular pathways and clinical application effects in AD and PD. It comprehensively analyzes technical bottlenecks, clinical transformation difficulties, ethical disputes and future optimized development directions, providing a reliable theoretical basis for subsequent basic experimental research and a standardized reference scheme for clinical transformation application of stem cell regenerative therapy.

2. Aging and cellular senescence

Physiological aging is a highly complex, comprehensive, and progressive biological process, accompanied by continuous decline of tissue and organ function, significant increase of disease susceptibility, gradual collapse of intracellular metabolic homeostasis and continuous disorder of immune regulatory balance [1, 2]. Cellular senescence is the core internal driving mechanism of individual systemic aging, which refers to irreversible permanent cell cycle stagnation caused by long-term oxidative stress, DNA damage and external adverse stress stimulation [5]. The main pathogenic factors promoting the aging process include continuous telomere attrition, frequent genomic DNA damage, excessive intracellular oxidative stress response, serious mitochondrial energy metabolism dysfunction, epigenetic modification abnormal changes and a persistent chronic low-grade inflammatory aging state [2].

Long-term excessive oxidative stress will induce a large number of reactive oxygen species to accumulate abnormally in neurons, directly damage neuronal nuclear DNA, structural proteins and mitochondrial ultrastructure, seriously interfere with normal intracellular energy synthesis and material metabolism balance, and further aggravate neuronal damage and apoptosis. Chronic inflammatory aging continuously activates brain glial immune cells, induces continuous secretion of

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a variety of pro-inflammatory cytokines, forms a vicious pathological inflammatory cycle, and greatly accelerates neuronal aging and apoptotic death. A large number of clinical statistical studies have confirmed that the expression level of peripheral systemic inflammatory markers is positively correlated with the onset risk, pathological progression severity, and prognosis outcome of Alzheimer's disease and Parkinson's disease [8].

MSCs can intervene and regulate a variety of classic aging signal pathways at the same time. They effectively upregulate telomerase activity to delay telomere shortening, reduce abnormal accumulation of reactive oxygen species, significantly enhance body antioxidant defense ability, maintain normal mitochondrial structural integrity and energy metabolic function, strongly inhibit excessive central inflammatory response, and actively clear accumulated senescent cells in tissues, so as to protect normal neural tissue structure integrity and significantly slow down the whole body physiological aging process [9].

3. Anti-aging functions of MSCs

3.1. Anti-inflammatory and immunoregulatory effects

MSCs can accurately and multi-directionally regulate a variety of key immune cells closely related to nerve aging and central lesion microenvironment. It effectively inhibits excessive abnormal activation of brain resident microglia, induces phenotypic transformation of pro-inflammatory M1 macrophages to anti-inflammatory repair-type M2 macrophages, significantly inhibits abnormal excessive proliferation of effector T lymphocytes, and remarkably enhances the immune suppression and regulatory function of regulatory T cells. At the same time, MSCs can downregulate the expression levels of pro-inflammatory factors, including TNF-α and IL-6, and upregulate the secretion of anti-inflammatory protective factors IL-10 and TGF-β, so as to continuously stabilize the immune homeostasis microenvironment of the central nervous system [10]. A persistent chronic low-grade inflammatory state is the core factor accelerating organism aging speed, a great deal of long-term clinical follow-up data show that MSCs targeted treatment can reduce systemic peripheral inflammatory marker levels by about 30%, and effectively relieve nerve tissue aging damage and pathological progression of neurodegenerative lesions [11].

3.2. Promoting tissue repair and regeneration

Under specific in vitro neural induction culture conditions, MSCs have obvious neural differentiation potential, can differentiate into typical neuron-like morphological cells, and normally express a variety of specific neuronal molecular markers. However, such induced differentiated neuronal cells have insufficient functional maturity, incomplete synaptic connection structure, and cannot form complete and effective functional neural circuits in vivo, which greatly limits the clinical application scope of direct stem cell replacement therapy. In practical neural lesion repair, MSCs mainly exert biological effects relying on powerful paracrine function, continuously secreting a variety of key neurotrophic factors including BDNF, GDNF, VEGF and HGF. Among them, BDNF effectively maintains normal neural synaptic plasticity, GDNF specifically protects dopaminergic neuron survival, VEGF significantly improves cerebral microcirculation blood supply, and jointly activates endogenous neural stem cells in brain tissue to participate in damaged nerve tissue repair and structural regeneration [7].

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3.3. Paracrine and exosome effects

MSC-derived exosomes are typical lipid bilayer nanoscale vesicles with a diameter of 30–150 nm, which are formed by budding of intracellular multivesicular bodies, and stably released into the extracellular environment after fusion with the cell plasma membrane [12]. Exosomes carry abundant active proteins, mRNA, microRNA and lipid biological molecules, have strong biological stability in vivo, and are not easily degraded by hydrolases in body fluids [7]. A large number of animal living imaging experimental studies have confirmed that MSC exosomes can smoothly cross the blood-brain barrier through a specific transcellular transport pathway, accurately target and gather in brain lesion areas, and play long-lasting, stable nerve protective biological effects [13]. Compared with traditional living cell transplantation treatment, exosome therapy has no tumorigenic risk, extremely low immunogenic rejection reaction, convenient storage and transportation conditions, and has gradually become the most ideal safe cell-free treatment preparation for clinical neurodegenerative diseases [11].

4. MSCs in neurodegenerative diseases

4.1. MSCs in Alzheimer's disease

The core pathological characteristics of AD include massive deposition of Aβ amyloid plaques, abnormal hyperphosphorylation of tau protein, formation of neurofibrillary tangles and extensive progressive loss of hippocampal and cortical neurons [4, 5]. MSCs effectively reduce abnormal Aβ plaque deposition by significantly upregulating the expression activity of insulin-degrading enzyme and neprilysin in brain tissue, and greatly enhance the phagocytic clearance ability of activated microglia to toxic aggregated Aβ substances [14]. Phase II clinical controlled trials confirmed that continuous intravenous MSC infusion for 6 months significantly reduced Aβ concentration in cerebrospinal fluid, effectively stabilized patient cognitive function and memory level, and had no serious adverse toxic side reactions. In addition, MSCs can significantly inhibit abnormal hyperphosphorylation of tau protein, reduce the formation of neurofibrillary tangles, relieve persistent central neuroinflammatory damage, and effectively delay the continuous cognitive decline process of AD patients [14].

4.2. MSCs in Parkinson's disease

PD pathological etiology is mainly caused by selective apoptosis of substantia nigra dopaminergic neurons and abnormal misfolding and aggregation of α-synuclein protein in the central nervous system. MSCs can continuously secrete high concentrations of GDNF and BDNF neurotrophic factors. GDNF effectively maintains long-term survival of dopaminergic neurons and normal synthesis and release of dopamine neurotransmitters. BDNF resists neuronal oxidative stress damage and stabilizes normal physiological function of dopaminergic neurons [15]. Randomized controlled clinical pre-research verified that striatal local MSC transplantation significantly improved patient motor function scores, effectively elevated brain dopamine content, remarkably relieved limb tremor, muscle stiffness and slow movement symptoms. Meanwhile, MSCs effectively inhibit abnormal aggregation of toxic α-synuclein protein, reduce central inflammatory cascade damage and slow progressive deterioration of PD neurological symptoms [15].

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5. Clinical trials and challenges

Although a large number of early short-term preliminary clinical trials have initially confirmed the basic safety and preliminary therapeutic potential of mesenchymal stem cell therapy in intervening aging-related neurodegenerative diseases, its large-scale standardized clinical translation, long-term clinical application and global popularization still face a series of complex, deep-seated and unresolved practical dilemmas and industry bottlenecks, which seriously restrict the transformation and development of this regenerative medical technology. Firstly, the inherent heterogeneity of MSCs from different sources is the most core and difficult problem, MSCs isolated from bone marrow, umbilical cord, placental tissue and adipose tissue have significant differences in cell surface marker phenotype, paracrine factor secretion ability, cell proliferation activity and multi-directional differentiation potential, coupled with the lack of unified cell isolation protocols, in vitro culture conditions, cell passage standards and quality detection indicators in global laboratories and research institutions, which directly leads to large fluctuations in clinical treatment efficacy, extremely poor repeatability of experimental research results, and cannot form a unified and objective clinical efficacy evaluation standard. Secondly, the survival and stable colonization rate of MSCs after in vivo transplantation is extremely low, most exogenous transplanted stem cells will be quickly recognized, attacked and cleared by the body's immune system within a short time after entering the body, and it is difficult to stably colonize and stay in the damaged area of the brain for a long time, so they cannot continuously exert stable anti-aging, anti-inflammatory and neuroprotective paracrine biological effects. Thirdly, the long-term systemic safety of MSC transplantation therapy has not been fully and systematically verified, there is still a serious lack of multi-year, large-sample and multi-center long-term follow-up clinical data, and potential safety risks such as stem cell ectopic differentiation, abnormal uncontrolled cell proliferation, local tissue lesion formation and potential tumorigenicity have not been fully studied and confirmed. In addition, prominent ethical disputes and imperfect regulatory systems have become important obstacles to clinical promotion, embryonic-derived MSCs involve widespread and intense ethical controversies, clinical informed consent procedures are not standardized, the ownership of biological tissue samples is vague, illegal commercial abuse and profit-making abuse of stem cell technology occur frequently, and the lack of unified international regulatory standards, quality evaluation norms and clinical operation guidelines further seriously hinders the joint research and global standardized clinical transformation of MSC therapy [6].

6. Future directions

In view of the series of key constraints restricting the clinical transformation and standardized application of MSCs, including serious cell source heterogeneity, extremely low post-transplantation survival and colonization rate, unclear long-term treatment safety, prominent ethical disputes and imperfect global collaborative supervision system, this paper puts forward a comprehensive, systematic, targeted and highly operable set of long-term optimization strategies to promote the safe, standardized and sustainable development of MSC anti-aging and neurodegenerative disease treatment. Firstly, it is urgent to establish a unified international whole-process standardized quality control and management system for mesenchymal stem cells, strictly formulate and unify the complete specification standards from cell source screening, in vitro amplification culture, cell purity and activity detection, safety index verification to clinical dosage setting and administration mode, so as to fundamentally solve the problem of unstable curative effect caused by cell heterogeneity and ensure the consistency and reliability of treatment effects. Secondly, adopt

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advanced and mature gene editing technology to carry out targeted optimization modification on MSCs, effectively enhance the brain targeting homing ability, anti-apoptotic performance and long-term in vivo survival time of stem cells, and comprehensively improve the efficiency and stability of transplantation therapy. Thirdly, vigorously develop and promote MSC-derived exosome cell-free treatment schemes, completely avoid the immune rejection, potential tumor risks and ethical disputes brought by living stem cell transplantation, and give full play to the unique advantages of exosomes that can easily cross the blood-brain barrier and exert long-lasting neuroprotective and anti-aging effects. Fourthly, apply cutting-edge 3D bioprinting technology to construct biomimetic neural scaffolds loaded with MSCs, improve the colonization rate and retention time of stem cells in brain lesion areas, and optimize the repair effect of damaged neural tissue. Finally, actively carry out large-sample, long-cycle and multi-center randomized controlled clinical trials to accumulate sufficient high-level evidence-based medical data, improve strict ethical review mechanisms, standardized informed consent processes and multi-departmental joint supervision systems, strictly curb irregular commercial application behaviors, and steadily promote the formal clinical transformation and standardized popularization of MSC therapy.

7. Conclusion

This study systematically sorts out and analyzes molecular mechanisms of organism aging and detailed therapeutic effects of MSCs on typical aging-related AD and PD neurodegenerative diseases. Research results fully show that MSCs can effectively delay systemic physiological aging and play powerful central nerve protective effects through multi-pathways, including immune balance regulation, damaged tissue repair and regeneration, and stable exosome paracrine signal transmission, having extremely important practical application value in clinical prevention and treatment of age-related neurodegenerative diseases. This paper comprehensively sorts out disease pathological molecular pathways, central immune regulatory mechanisms, biological characteristics of MSC exosomes and reliable clinical research evidence, systematically summarizes key challenges, including stem cell heterogeneity, low in vivo cell survival rate, unclear long-term safety, frequent ethical disputes and imperfect international supervision system. Corresponding optimization countermeasures, including unified industry standard system construction, exosome targeted treatment, accurate gene modification and novel 3D printed neural repair scaffolds, are put forward one by one. Although current MSC regenerative treatment still has many application limitations, with continuous technological innovation and standardized rigorous clinical research, MSCs will gradually become a mainstream key regenerative treatment scheme for aging-related neurological diseases, providing brand-new effective intervention schemes for global elderly healthy aging management and neurodegenerative disease clinical treatment.

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