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Stem Cell Therapy for Spinal Cord Injury

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Abstract:

Spinal cord injury (SCI) represents a debilitating neurological condition with a rising incidence, posing serious threats to patients' quality of life and their ability to engage in social activities. Despite some symptomatic relief and disease-modifying effects offered by conventional therapies, their capacity to facilitate neural regeneration and restore lost functions remains limited. In recent years, neural stem cells (NSCs) have emerged as a promising avenue in the field of SCI repair, owing to their inherent abilities of self-renewal and multilineage differentiation. NSCs contribute significantly to the reconstruction of damaged spinal tissue by modulating the local microenvironment, supporting remyelination, and enhancing neural recovery through a combination of cell replacement, secretion of neurotrophic molecules, and immunoregulatory mechanisms. This review provides a comprehensive overview of the roles and mechanisms by which NSCs participate in SCI repair, along with commonly used evaluation strategies such as imaging techniques, electrophysiological measurements, and behavioral assessments. However, the clinical translation of NSC-based therapies remains constrained by several unresolved issues, including the poor survival of grafted cells, variable neuronal differentiation rates, potential oncogenic risks, and heterogeneous outcomes across different injury models. These findings offer deeper insights into the pathophysiology of SCI and lay a theoretical foundation for developing innovative approaches to stem cell-based interventions in clinical settings.

Keywords:-Spinal cord injury; spinal cord injury; neural stem cell

I. Introduction

Spinal cord injury (SCI) is a highly disabling neurological disease, and its incidence rate is increasing year by year worldwide, seriously affecting the life and work of patients. According to statistics from the World Health Organization, there are about 250,000 to 500,000 new cases of SCI each year in the world, and traffic accidents, industrial accidents, falls and sports injuries are the main causes. In China, with the

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acceleration of urbanization and the strengthening of the aging trend of the population, the incidence of SCI is also on the rise. According to epidemiological surveys, the majority of SCI patients in my country are young and middle-aged men, and most of them are concentrated in high-risk occupational groups such as construction workers and motor vehicle drivers. This not only increases the burden on the medical system, but also has a profound impact on the patients' families and social economy.

The motor, sensory and autonomic dysfunction caused by SCI is essentially due to the irreversible destruction of the neural tissue structure. Although traditional treatments can relieve symptoms and delay deterioration to a certain extent, their effects in promoting nerve regeneration and restoring function are still limited. The regenerative capacity of the spinal central nervous system is weak, and there are inhibitory factors in the local environment, such as inflammatory response, glial scar formation, free radical damage, etc., making the effective treatment of SCI always a major challenge facing modern medicine.

In this context, the application of stem cell therapy in the repair of SCI has gradually become the frontier focus of current regenerative medicine and neuroscience research. This study will focus on neural stem cells and explore their biological characteristics, self-renewal and multidirectional differentiation mechanisms to explore their role in SCI, including cell replacement, secretion of nutritional factors, regulation of immune response, and promotion of myelin regeneration. At the same time, this article will also introduce the evaluation methods of the therapeutic effect after neural stem cell transplantation, such as imaging analysis, electrophysiological testing, and behavioral function testing, in order to fully present the scientificity and feasibility of neural stem cell therapy.

This study helps to deepen the understanding of the pathophysiological changes after SCI at the basic theoretical level, and provide theoretical support for intervention treatment; and explore the path of neural stem cell treatment for SCI from a clinical perspective, providing new treatment options for patients.

II. INTRODUCTION of SCI

SCI is mainly caused by direct physical damage and a series of pathological processes triggered in the subsequent stages. Its stages can be mainly divided into primary injury and secondary injury.

Primary injury is direct physical damage, which is generally caused by acute external force (such as impact, traction, etc.), which will cause traumatic impact on the spinal cord, causing damage including but not limited to damage to the axon network and glial membrane. In fact, the severity of SCI mainly depends on the degree of initial injury and the subsequent compression of the spinal cord. The damage to the nerve tissue caused by it will trigger a series of subsequent secondary injuries and other events.

The initial injury will cause calcium ions to accumulate continuously in the human body, thereby causing neuronal excitotoxicity, increasing the levels of glutamate and reactive oxygen in the human body, damaging phospholipids and protein molecules, and ultimately leading to neurological dysfunction, inflammation, edema, vascular damage and other clinical symptoms [1].

The pathological mechanism of SCI includes a series of chain events, which are interrelated. Therefore, in some cases, it is precisely because of its complex pathological mechanism that it leads to difficult clinical situations.

Common spinal cord injuries are prone to extensive bleeding and neurogenic shock, which can lead to interruption of the blood supply to the spinal cord and symptoms of hypotension. Damage to capillaries promotes the extravasation of white blood cells and red blood cells. Changes in osmotic pressure further damage blood vessels and even cause vasospasm, ultimately leading to cell necrosis and tissue damage.

In the case of SCI, the balance between intracellular solutes and water flow is disrupted, which in turn causes a variety of symptoms such as ionic and vasogenic edema, and produces free radicals and glutamate.

SCI causes a large increase in glutamate concentration, which can lead to a variety of more serious follow-up events such as over-activation of the influx of sodium and calcium ions and mitochondrial dysfunction [2].

III. Neural Stem Cells (NSCs)

NSCs demonstrate significant therapeutic potential for SCI repair due to their unique self-renewal capacity and multipotent differentiation capabilities. Under physiological conditions, NSCs maintain neural homeostasis through symmetric division to expand the stem cell pool or asymmetric division to generate differentiated progeny. This dynamic equilibrium is tightly regulated by niche-derived signals. For instance, stem cell niches in the hippocampal dentate gyrus and subventricular zone provide critical growth factor support (e.g., EGF, bFGF), while core transcription factors like Oct4 and Sox2 sustain their undifferentiated state.

Following pathological insults such as SCI, endogenous NSCs exhibit activated proliferation and migration; however, their intrinsic repair capacity is often insufficient due to inhibitory microenvironmental factors (e.g., glial scar formation, inflammatory cytokine release). Consequently, exogenous NSC transplantation has emerged as a pivotal strategy to enhance neural regeneration [3].

The differentiation fate of NSCs is precisely modulated by

microenvironmental cues: Wnt/β-catenin signaling promotes neuronal differentiation, whereas BMP pathways favor astrocytic lineage commitment. In SCI models, transplanted NSCs adapt to local microenvironmental changes, differentiating into functional neurons, oligodendrocytes, and astrocytes to facilitate neural circuit reconstruction. For example, in contusion-type SCI rat models, grafted NSCs differentiate into glutamatergic neurons, forming synaptic connections with host neurons and partially restoring motor function. Additionally, oligodendrocyte differentiation supports remyelination to improve conduction velocity, while astrocytes enhance neuronal survival by regulating local metabolism and ion homeostasis. These properties establish NSCs as an ideal candidate for SCI repair [3,4].

IV. Principles of Neural Stem Cell Transplantation

Although adult mammalian neurons exhibit limited regenerative plasticity, their repair capacity is severely restricted in the central nervous system (CNS) due to terminal differentiation and inhibitory post-injury microenvironments (e.g., glial scarring, neuroinflammation).

NSC transplantation promotes SCI repair through multiple mechanisms, with cell replacement being the most direct strategy. Studies demonstrate that grafted NSCs can differentiate into functional neurons integrated into host neural networks. For instance, in complete spinal transection models, human NSCs differentiate into motor neurons, extending axons distal to the lesion and forming neuromuscular junctions to partially restore limb motor function. Moreover, NSC-derived oligodendrocytes enable remyelination of denuded axons, improving signal conduction.

Beyond cell replacement, NSCs exert therapeutic effects via paracrine actions. They secrete neurotrophic factors (e.g., BDNF, GDNF, NGF) that enhance host neuron survival, axonal regrowth, and synaptic plasticity. In chronic SCI models, elevated BDNF levels from transplanted NSCs promote corticospinal tract regeneration and fine motor recovery. NSCs also exhibit immunomodulatory properties, polarizing microglia/macrophages toward the pro-repair M2 phenotype and suppressing excessive inflammation. Single-cell RNA sequencing reveals reduced pro-inflammatory cytokines (TNF-α, IL-6) and elevated anti-inflammatory factors (IL-10, TGF-β), fostering a regeneration-permissive niche. These synergistic mechanisms underscore NSC transplantation as a potent SCI treatment strategy [5-7].

In summary, NSCs represent a promising therapeutic cell source due to their dual capacities for self-renewal/differentiation and multifaceted repair mechanisms in neurological disorders.

V. Principles of stem cell therapy for SCI

NSCs play a pivotal role in maintaining cerebrospinal fluid dynamics and act as a physiological barrier within the central nervous system. In the context of spinal cord injury (SCI), NSCs exert their therapeutic effects through several mechanisms. One critical mechanism involves their differentiation into neurons, which can either replace the lost neural population directly or reconstruct neural circuits that facilitate electrical signal conduction across the lesion. Studies have demonstrated that injured axons can establish connections with grafted NSCs, creating relay circuits that potentially restore disrupted neural pathways. These transplanted neurons not only attract regenerating host axons but also extend their own projections, forming new synaptic relationships with host neurons.

In addition, NSCs secrete various neurotrophic factors, including BDNF, GDNF, CNTF, IGF-1, NGF, and HGF, which help modulate the injury microenvironment, support neuronal survival, and attenuate neuroinflammation. For instance, CNTF encourages oligodendrocyte maturation, IGF-1 supports neuronal viability and functional improvement, while GDNF and HGF contribute to synaptogenesis and anti-inflammatory responses. Animal studies have confirmed that NSCs expressing these factors enhance motor recovery and promote plasticity, underscoring their neuroprotective capacity in SCI repair [8].

NSCs also support remyelination and improve motor and sensory outcomes by promoting oligodendrocyte lineage differentiation and limiting the expansion of post-injury glial scarring through structural integration. Their immunomodulatory function includes reducing CD4+ T cell numbers and shifting microglial phenotypes from pro-inflammatory to neuroprotective states, thereby alleviating secondary demyelination and tissue damage.

Following SCI, endogenous neural stem/progenitor cells (NSPCs)—such as ependymal cells and NG2-positive oligodendrocyte precursor cells (OPCs)—are rapidly activated. These cells undergo asymmetric division and, alongside reactive astrocytes, contribute to the formation of a glial scar border. While glial scarring serves to protect remaining tissue, prevent excitotoxicity, and remove cellular debris, excessive inflammation and physical barriers may hinder axon regeneration and cell migration, limiting recovery.

Although NSCs tend to differentiate into astrocytes under SCI conditions, the presence of exogenous growth factors like bFGF, EGF, and PDGF-AA can steer their differenti-

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ation toward the oligodendrocyte lineage, thus promoting remyelination. Experimental models involving rats, dogs, and marmosets have demonstrated that NSC-derived oligodendrocytes are capable of reconstructing myelin sheaths and restoring neural conduction. Moreover, by secreting neurotrophic factors and forming cellular scaffolds, NSCs can induce regeneration of corticospinal and serotonergic axons, enhance synaptic integration, and facilitate neural circuit reconstruction. Overexpression of GDNF has been particularly associated with improved myelination and axonal repair.

In summary, NSCs promote functional recovery through the dual regeneration of axons and myelin. Their integration into injured spinal cord tissue forms the foundation for circuit reconstruction, making them a promising tool in the treatment of spinal cord injuries [9].

VI. Therapeutic Outcome Evaluation Metrics and Methods

The efficacy of NSC therapy for SCI requires multidimensional assessment, including functional recovery, histological repair, and microenvironmental modulation. For motor function, behavioral tests (e.g., BBB score, gait analysis) serve as gold standards. In rat contusion models, NSC-treated groups show significantly higher BBB scores (12.5±1.2 vs. 6.8±0.9 at 8 weeks) and 78% recovery in hindlimb coordination, correlating with neuromuscular junction formation by graft-derived motor neurons.

Advanced imaging and electrophysiology provide structural/functional evidence: Diffusion tensor MRI reveals 40% greater white matter integrity in treated groups, indicating axonal regrowth and remyelination. Motor/somatosensory evoked potentials confirm improved conduction velocity. Histologically, NSC transplantation increases vascular density by 2.3-fold and myelinated axons by 60%, with synaptic integration into host circuits.

Microenvironmental regulation is another critical metric. Single-cell analyses show M2 microglial polarization increasing to 67% (vs. 32% in controls), alongside >50% reduction in pro-inflammatory cytokines (TNF-α, IL-1β). This immunomodulation strongly correlates with motor recovery ($r=0.82$, $p<0.01$), highlighting its central role in repair. Collectively, these metrics demonstrate NSC therapy's efficacy in neural regeneration, functional restoration, and niche optimization [10].

VII. CONCLUSION

This review systematically examines NSC mechanisms and evaluation methods for SCI repair. Research confirms that NSCs drive structural/functional recovery through tripartite actions: cell replacement, neurotrophic secretion, and immunomodulation. These findings deepen understanding of CNS regeneration while informing clinical translation. However, limitations persist, including low graft survival rates (<30%), variable neuronal differentiation efficiency (20–65%), and unresolved long-term safety/oncogenic risks. Differential responses across injury models (acute vs. chronic) also require clarification.

VIII. Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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