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Stem Cells and Optic Nerve Injury Repair

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Abstract. Nerve injuries are a prevalent category of neurological disorders with diverse etiologies. Despite timely medical intervention, full functional recovery remains elusive due to the inherently limited regenerative capacity of neural cells. Traditional treatments often fall short in promoting true nerve regeneration. Stem cells, characterized by their multipotent differentiation potential, offer a novel approach by providing the possibility of replacing damaged neural cells. This paper reviews the current challenges in nerve injury treatment and discusses the advantages and limitations of stem cell therapy, with a focus on the optic and spinal nerves. Particular attention is given to different types of stem cells, their mechanisms of action, and potential clinical applications.

Keywords: Stem Cells, Optic Nerve Injury Repair, Nerve injury

1. Introduction

Nerve injury is a common condition in clinical surgery, often resulting in significant sensory and motor dysfunctions that can lead to lifelong disability. Damage to motor nerves may cause muscle atrophy and impair movement, making basic activities such as walking or grasping difficult. Sensory nerve injury, on the other hand, may lead to hypoesthesia or hypersensitivity, increasing the risk of accidental injury due to altered responses to temperature, pain, and other stimuli.

Currently, autologous nerve grafting remains the primary method for nerve repair. However, it suffers from major limitations, including limited donor availability, complications at the donor site, and unpredictable outcomes. Among various types of nerve injuries, optic nerve damage—especially in the context of glaucomatous optic neuropathy—presents unique challenges. Glaucoma is primarily caused by elevated intraocular pressure (IOP), which results in mechanical compression and impaired blood supply to the optic nerve, leading to progressive visual field loss. Patients often experience tunnel vision, where peripheral vision is lost while central vision remains, eventually culminating in blindness if untreated. Early symptoms are subtle and may include mild discomfort or headache, while advanced stages significantly impair daily functioning, such as reading or navigating through space.

The treatment of optic nerve injury faces two major obstacles. First, as part of the central nervous system, the optic nerve exhibits extremely limited regenerative potential due to both cellular and microenvironmental factors. Second, many optic nerve diseases have complex and multifactorial etiologies that are difficult to fully control. In the case of glaucoma, while medications, laser therapy, and surgery can help reduce IOP, they rarely reverse existing nerve damage, and

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fluctuations in IOP can continue to exacerbate injury. Moreover, no pharmacological agents are currently available that can directly promote the repair or regeneration of the damaged optic nerve. As a result, current treatments largely aim to alleviate symptoms and slow disease progression, rather than provide a cure.

In recent years, stem cell technology has emerged as a promising therapeutic strategy for nerve injury. Studies have shown that stem cells can be administered directly or pre-differentiated in vitro prior to transplantation. Beyond cellular replacement, stem cells can also secrete exosomes containing neurotrophic and anti-inflammatory factors, which support neuronal survival and modulate the injury environment—an approach referred to as cell-free therapy. Certain stem cells also exhibit homing capabilities, allowing them to migrate toward injury sites and exert localized therapeutic effects. Despite ongoing challenges such as limited stem cell sources, ethical concerns, and a lack of large-scale clinical trials, the continued advancement of stem cell research holds significant potential. As such, stem cell therapy is rapidly becoming a focal point in the field of neuroregenerative medicine.

2.Nerve injury and repair

Nerve injury is a common surgical condition with a wide range of causes, including metabolic disorders, malignant tumors, endogenous or exogenous toxins, as well as thermal, chemical, or mechanical trauma [1]. Such injuries can impair both sensory and motor functions, and in severe cases, may result in lifelong disability, significantly reducing a patient's quality of life and causing substantial inconvenience and suffering.

Currently, the most effective method for nerve repair is autologous nerve grafting. However, this approach has several limitations, such as poor functional recovery due to nerve mismatch, limited availability of donor nerves, denervation at the donor site, and size discrepancies between donor and recipient nerves [2].

Stem cells—characterized by their ability to self-renew and differentiate into multiple cell lineages—offer a promising alternative for nerve repair. They can differentiate into neurons and Schwann cells, both critical for neural regeneration, and secrete exosomes that promote cellular repair and regeneration. With increasing research into the application of stem cells in nerve repair, this review aims to summarize the recent advances in this field.

3. Stem cells and their role in injury repair

3.1. Classification of stem cells

Stem cells are a unique class of cells capable of self-renewal and multilineage differentiation(table 1). Due to these distinctive biological properties, they present novel therapeutic strategies for treating organ and tissue injuries, degenerative diseases, complex disorders, and slowly regenerating neural damage. Based on their developmental stage, stem cells are generally classified into three types: embryonic stem cells, embryonic germ cells, and adult stem cells [3][4].

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Table 1: Comparison of embryonic, fetal germ, and adult stem cells

Category	Embryonic Stem Cells	Fetal Germ Cells	Adult Stem Cells
Source	Derived from the inner cell mass of the blastocyst	Derived from fetal gonadal tissue	Derived from adult tissues such as bone marrow, blood, etc.
Differentiation Potential	At early embryonic stages, they are pluripotent and can differentiate into all types of cells from the three germ layers	Capable of differentiating into various cell types of the embryo but may lose pluripotency after prolonged culture or depending on developmental stage	Generally unipotent or multipotent; limited to differentiating into specific cell types of the tissue they are derived from
Morphological Features	Typically round, tightly packed colonies with high nuclear-to-cytoplasmic ratio	Similar to embryonic stem cells but slightly more differentiated, some changes in colony morphology	Morphology varies by tissue of origin, with less tightly packed colonies
Biological Characteristics	(1)Pluripotent; (2)Capable of indefinite self-renewal	(1) Pluripotent; (2) Self-renewal ability weaker than embryonic stem cells	(1) Usually unipotent or multipotent; (2)Limited self-renewal capacity

3.2. Mechanisms of neural repair by stem cells

Early studies on stem cell-based neural repair primarily focused on inducing stem cells to differentiate into neural cells to replace damaged ones. However, as research has advanced, it has been discovered that stem cells not only possess the potential to differentiate into neural cells but also secrete neurotrophic factors that promote tissue repair and reduce inflammation at the injury site. This dual functionality has garnered increasing attention toward stem cells as a promising therapeutic option for neural injury repair [1].

One key advantage of stem cells lies in their capacity for self-renewal, which enables the generation of a sufficient number of target cells to act on damaged regions. Upon migration to injured neural tissue, stem cells continue to proliferate and, under suitable microenvironmental conditions, differentiate into the required cell types [5]. Approximately 5% of bone marrow stromal cells can spontaneously transdifferentiate into Schwann-like cells without specific interventions. Furthermore, beyond cell differentiation, the neurotrophic effects of stem cells involve the secretion of bioactive neurotrophic factors that create a favorable microenvironment for the survival and regeneration of neurons. For example, adipose-derived stem cells may inhibit caspase-3 activity in a neurotrophin-dependent manner, thereby reducing dorsal root ganglion damage.

The effectiveness of stem cell transplantation is also influenced by the levels of growth factors in the microenvironment. Studies have shown that neutralizing antibodies against nerve growth factor can abolish the axonal growth-promoting effects of bone marrow stromal cells on sensory and sympathetic nerves in vitro. Similarly, antibodies against brain-derived neurotrophic factor (BDNF) can attenuate the regenerative influence of adipose-derived stem cells [6].

4. Optic nerve injury and stem cell-based repair

4.1. Optic nerve injury and treatments

The optic nerve is composed of axons from retinal ganglion cells and is a vital component of the human nervous system, responsible for transmitting visual information from the retina to the brain. Common causes of optic nerve damage include glaucoma, traumatic injuries, genetic disorders, and

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neurodegenerative diseases [7]. Such damage can result in visual impairment or even blindness, significantly affecting quality of life. Optic nerve damage typically arises from the disruption of neural connections and glial cell dysfunction, which impairs their supportive role for neurons. Due to the non-regenerative nature of retinal ganglion cell axons, effective treatments for optic nerve damage remain elusive [8]. Currently, only drugs and surgical interventions can alleviate symptoms. However, stem cell therapy offers a new avenue by potentially replacing apoptotic and damaged cells.

4.2. Stem cell therapies for optic nerve injury

4.2.1. Embryonic stem cells

Embryonic stem cells (ESCs) can differentiate into photoreceptor cells in the retinal environment. Early methods involved direct injection of ESCs into the vitreous cavity of mouse eyes, though many cells failed to reach the injury site. Later research enabled more precise delivery into the subretinal space, significantly improving therapeutic outcomes [9]. Fluorescent labeling and in vitro differentiation techniques have also isolated cells exhibiting retinal ganglion cell characteristics, supporting the feasibility of using in vitro cultured ESCs to treat neural injuries [4].

4.2.2. Adult stem cells

Mesenchymal stem cells (MSCs) possess multipotent differentiation capabilities and can secrete growth factors, cytokines, chemokines, and proteases that contribute to tissue repair. In experiments involving MSC injections into the eyes of mice, increased levels of inflammation-related and neuroregenerative factors were observed after one week, along with improved survival of retinal ganglion cell synapses. The upregulation of growth-associated protein 43 (GAP-43) and hypoxia-inducible factor-1α (HIF-1α) suggested that MSCs enhance synaptic survival through these factors [4].

Based on their characteristics, MSCs can be utilized via two therapeutic approaches: cell-based therapy and cell-free therapy.

Cell-Free Therapy: Relies on exosomes and extracellular vesicles (EVs) containing proteins, mRNA, and miRNA secreted by MSCs. Due to their small size, these vesicles can more easily penetrate retinal ganglion layers. Studies have shown that exosome injection into the vitreous cavity improves retinal ganglion cell survival for up to a month [10].

Cell-Based Therapy: Involves direct injection of MSCs into the vitreous cavity, where most remain and secrete neurotrophic factors. Intravenous injection has also shown potential—though the cells do not reach the injured eye directly, they modulate the microenvironment to protect retinal ganglion cells.

5. Spinal cord injury and stem cell repair

5.1. Spinal cord injury and current treatments

Spinal cord injury (SCI) is a severe central nervous system disorder. Current treatment strategies mainly include rehabilitation and pharmacological interventions. However, due to the poor regenerative capacity of spinal nerve fibers, clinical outcomes remain unsatisfactory. Stem cell therapies offer hope by potentially overcoming the regenerative limitations of spinal cord tissue.

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These therapies aim to: ① Inhibit secondary injury ② Reduce inflammation ③ Promote remyelination④ timulate axonal regeneration⑤ Prevent scar formation [11].

5.2. Stem cell therapies for sci

5.2.1. Embryonic stem cells

Due to their pluripotency, ESCs can be genetically modified to differentiate into oligodendrocytes and neural progenitor cells. Neural progenitors can replace damaged neurons, while oligodendrocytes facilitate remyelination and improve neural signal transmission. ESCs also secrete neurotrophic factors that promote neuron regeneration and inhibit secondary injury [12].

5.2.2. Adult stem cells

The main adult stem cells used for SCI treatment are neural stem cells (NSCs) and mesenchymal stem cells (MSCs).

Neural Stem Cells: Transplanted into injured spinal cord regions, NSCs can differentiate into neurons, replacing those lost due to injury [13]. NSCs also reduce inflammation. Comparative studies between saline-treated and neural progenitor-treated SCI models have shown lower expression of pro-inflammatory cytokines in the latter. Additionally, NSCs secrete neurotrophic factors such as CNTF and BDNF, improving the microenvironment [14]. However, some studies indicate that transplanted NSCs may undergo morphological changes and rupture over time, diminishing their therapeutic effect. Enhancing post-transplantation survival of NSCs is a key challenge [15].

Mesenchymal Stem Cells: Bone marrow-derived MSCs can be induced in vitro to differentiate into neurons and glial cells. They can also promote regeneration through paracrine signaling. For example, exosomes from umbilical cord MSCs can shift macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 state, reducing levels of TNF-α, IFN-γ, and IL-6. MSCs also downregulate pro-apoptotic protein caspase-3 while upregulating anti-apoptotic proteins, mitigating secondary injury. Moreover, MSC-derived exosomes can promote angiogenesis and synaptogenesis [16].

Current stem cell transplantation methods mainly rely on local injection to ensure therapeutic effects. However, direct injection risks exacerbating injury. Intrathecal injection via cerebrospinal fluid has emerged as a more viable method, using CSF flow to transport stem cells to the injury site.

6. Conclusion

In recent years, stem cell transplantation has been shown to be a safe and feasible approach for repairing optic nerve injuries. However, more specific studies targeting optic nerve damage are still lacking, and there is an absence of systematic analyses regarding the potential effects of stem cell transplantation on the body. Additionally, existing studies are limited by small sample sizes and narrow disease categories. At present, the repair of optic nerve injuries remains an area in urgent need of new methods and breakthroughs. Closer integration between basic research findings and clinical practice is essential to advance the development of this field.

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