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Stem Cell Therapies for Spinal Cord Injury - A Review

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Abstract

The escalating incidence of Spinal Cord Injury (SCI), with approximately 0.9 million cases globally, underscores its growing public health concern. Traumatic SCI, often prevalent in developing nations due to factors like motor vehicle accidents and falls, leads to secondary damage involving inflammation, neuronal death, and ionic dysregulation. Despite the absence of an effective treatment for SCI, Stem Cell Therapy (SCT) emerges as a promising avenue, harnessing stem cells' unique capabilities for regeneration and replacement. The review explores various stem cell types, such as Neural Stem/Progenitor Cells (NS/PCs), Embryonic Stem Cells (ESCs), Induced Pluripotent Stem Cells (iPSCs), and Mesenchymal Stem Cells (MSCs), detailing their potential in preclinical and clinical contexts. Specifically, NSCs exhibit therapeutic promise by modulating astrocyte contribution, enhancing differentiation, and promoting growth factors. ESCs, despite their pluripotency, face ethical concerns and potential teratocarcinoma formation. IPSCs, reprogrammed from somatic cells, showcase potential in treating SCI without ethical issues. MSCs, with diverse sources like bone marrow, umbilical cord, and adipose tissue, offer versatility in differentiation and therapeutic benefits. Clinical

trials with MSCs, especially BM-MSCs, UC-MSCs, and AD-MSCs, demonstrate improvements in motor and sensory functions, highlighting their regenerative potential. Despite promising results, challenges such as potential tumorigenesis and high costs persist, warranting further exploration and clinical translation of these stem cell therapies for SCI.

Keywords: „Stem Cells", „Spinal Cord Injury", „SCI", „Regenerative Medicine", „Neural Stem Cells", „NSCs", „Embryonic Stem Cells", „ESCs", „Induced Pluripotent Stem Cells", „IPSCs", „Mesenchymal Stem Cells", „MSCs".

Introduction

Spinal cord injury (SCI) represents a profound neurological disorder, resulting in the temporary or permanent impairment of sensory, motor, and autonomic nerve functions, as also in social, physical and psychological damage to patients [1]. The incidence and impact of SCI have escalated over the past three decades, presenting a growing public health concern [2]. Notably, males and the elderly experience a higher prevalence of SCI compared to females and younger individuals [2]. As of now, the global incidence stands at approximately 0.9 million cases [2]. Spinal cord injury (SCI) can occur because of two main reasons: traumatic and non-traumatic. The primary reasons for traumatic spinal cord injuries (TSCI) in developing nations are often linked to motor vehicle accidents (43%), falls (34%), gunshot wounds (10%), incidents of violence (5%), and sports-related activities (2%) [3], while a non-traumatic SCI, which is significantly less common, typically results from degenerative diseases, congenital anomalies (like spina bifida) and various types of tumors, including both primary neoplasms and cancer metastasis [4][5][6]. Pathophysiologically - the majority of damage to the nervous system after a traumatic event comes from various secondary factors, involving molecular processes like inflammation, the death of nerve cells, imbalances in ionic levels, free radicals and lipid peroxidation [7]. Other contributing factors include the disruption of regular nerve pathways, problems with the blood–brain barrier, cell self-destruction (apoptosis), and tissue death (necrosis) [7]. This is often followed by processes like cavitation and retrograde degeneration [7]. For traumatic spinal cord injuries, surgical decompression appears crucial in preventing

further harm, typically recommended within 8 to 24 hours after the injury, paired with spinal fixation, ensuring proper support for nursing and rehabilitation efforts. This treatment aims to protect whatever neurological abilities are left, without necessarily bringing back lost functions. This is especially important for patients dealing with severe paralysis [8][9].

Unfortunately, so far, there hasn't been a treatment that can effectively treat spinal cord injuries and enhance the outlook for patients with SCI. Stem Cell Therapy (SCT) is a new treatment filled with hope and potential progress. It has developed because the current medications to control neuroinflammation and protect nerves don't reach the best standard of treatment for spinal cord injuries. SCT offers a hopeful outlook for potential neurological improvement in patients with disabilities following spinal cord injuries. It is an evolving treatment approach that harnesses the unique abilities of stem cells, such as their capacity to transform into different cell types, release beneficial substances, and renew themselves. This process aims to regenerate or replace damaged cells and tissues in the spinal cord [10]. Stem cells are commonly categorized as either adult (somatic) stem cells or embryonic stem cells, depending on their origin. Another way to classify them is by their potency, which refers to their capacity for cell differentiation into various types. There are different potency levels, including totipotent (capable of forming a complete organism), pluripotent (able to differentiate into any cell type except placental tissues), multipotent (limited but significant differentiation potential within a specific tissue or organ), oligopotent (similar to multipotent), and unipotent (with the least differentiation capacity, producing only one specific cell type) [11].

This review aims to provide an overview of the current state of stem cell treatments in the context of spinal cord injury, exploring preclinical advancements, clinical trials, and the challenges and prospects associated with this evolving therapeutic approach.

Material and Methods

The purpose of this study is to review the available data on Stem Cell Therapies in Spinal Cord Injury. We reviewed the literature available in medical research databases PubMed and Google Scholar. The keywords used in the title or in the body were: „Stem cells”, „spinal cord injury”, „SCI”, „epidemiology”, „traumatic spinal cord injury”, „non-traumatic spinal cord injury”, „regenerative medicine”, „Neural Stem Cells”, „NSCs”, „Embryonic Stem Cells”, „ESCs”, „Induced Pluripotent Stem Cells”, „IPSCs”, „Mesenchymal Stem Cells”, „MSCs”.

We focused on full-text articles about the treatment of Spinal Cord Injury using Stem Cells.

Stem Cell Types, Sources and Possibilities

Neural Stem/Progenitor Cells (NS/PCs)

Neural stem cells (NSCs) and neural progenitor cells (NPCs) are specialized adult stem cells uniquely capable of differentiating into the three essential neural cell types: astrocytes, oligodendrocytes, and neurons. These cells reside in specific regions, namely the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus in the hippocampus [12].

The therapeutic effects of NSCs in neurological diseases involve several mechanisms. Firstly, NSCs modulate the contribution of astrocytes to the glial scar, enhancing the differentiation of oligodendrocytes and neurons, contributing to the replacement of missing nerve cells in SCI. Additionally, NSCs secrete pro-regenerative factors, including BDNF, CNTF, GDNF, NGF, and IGF-1, which protect damaged tissue cells and neuritis [13][14][15].

In the treatment of SCI animal models, NSCs have shown significant promise, particularly in spinal crush injury models. Transplantation of NSCs into damaged spinal cord tissue promotes the recovery of body function through a dual approach. Firstly, NSCs entering the injured area differentiate into neurons, directly replacing lost neurons or providing a neuronal substrate to bridge the lesion area [16][13][17]. Secondly, NSCs secrete growth-promoting factors that enhance the survival and growth of damaged neurons [18].

Key observations include accelerated axonal growth and improved axonal conduction after NSC transplantation. NSCs also play a role in promoting oligodendrocyte differentiation, addressing demyelination observed in SCI and subsequently enhancing myelination [19]. Moreover, NSCs contribute to the formation of a glial scar, restricting the secondary enlargement of the lesion and preventing further expansion after the initial insult [20]. The therapeutic effects of NSC transplantation extend to immunomodulation, regulating T cells and macrophages to inhibit inflammatory demyelination [21]. While the safety of NSC transplantation has been established, its effectiveness in improving patient function remains a subject of debate.

Embryonic Stem Cells (ESCs)

Embryonic cells possess pluripotent capabilities, making them intriguing for treating traumatic spinal cord injuries. ESCs have found applications in treating various diseases, including nerve damage and neurodegenerative conditions. Their pluripotent nature, capable of differentiating into all types of tissue cells, especially neurons, positions them as a potent option for replacing neuronal cells in the treatment of related disorders. The use of ESCs for treating SCI primarily involves employing differentiated neurons and glial cells from ESCs to address the cell defects resulting from SCI [22]. This approach, combined with the secretion of active factors, aims to hinder further damage, promote nerve tissue regeneration, and ultimately achieve therapeutic and reparative goals [23].

Transplanting pre-differentiated ESCs into rat and monkey SCI models has shown substantial improvement in motor dysfunction in these animals [24][25][26].

Clinical trials show that oligodendrocyte progenitor cells derived from human ESCs are safe to transplant in patients with spinal cord injury. Additionally, studies revealed improved body functions in SCI patients following intervention with human ESCs, with no reported serious complications [27][28][29].

However, research also indicates their potential involvement in teratocarcinoma formation [30]. Additionally, the ethical dilemma arises as these cells are sourced from living human embryos, prompting global ethical concerns [31].

Induced Pluripotent Stem Cells (IPSCs)

Induced Pluripotent Stem Cells exhibit pluripotent characteristics comparable to Embryonic Stem Cells. They are created through the reprogramming of somatic cells, typically obtained from easily accessible tissues like autologous skin. This method not only sidesteps ethical concerns but also enables autologous cell transplantation, reducing the risk of rejection. Originally obtained from mouse cells, iPSCs were successfully generated from fibroblasts by introducing four factors simultaneously (Oct4, Sox2, Klf2, and c-Myc) [32]. A similar strategy has been applied to generate human iPSCs from human fibroblasts, utilizing an alternative set of factors, including Oct4, Sox2, Nanog, and Lin28 [33]. While iPSCs and ESCs each present

unique cytological advantages, a shared limitation lies in the potential risk of carcinogenesis. This risk results from their inherent pluripotency, which may become unregulated following transplantation [34].

Neural stem cells (NSCs) derived from transplanted iPSCs contribute to remyelination, axonal regeneration, and the release of neurotrophic factors, concurrently mitigating inflammation [35]. Previous research indicates the safety and efficacy of orthotopic iPSC transplantation as a therapeutic approach for spinal cord injury (SCI). This involves inducing iPSC differentiation into oligodendrocytes or neurons before retransplantation into spinal contusion models of rats and mice [36][37]. Notably, significant improvements in motor function defects were observed within 3 to 5 weeks, with no instances of tumor formation.

Neural progenitors (NPs) obtained from a human iPSCs clone played a crucial role in restoring the injury site. These iPSC-derived neural stem/progenitor cells (iPSC-NS/PCs) not only prevented demyelination but also facilitated synapse formation and the secretion of neurotrophic factors [38][39][40][41]. This concerted effort resulted in enhanced functional recovery in monkey model for spinal cord injury (SCI), all achieved without the formation of tumors [42].

Contrastingly, there are studies indicating that human iPSC may not yield favorable outcomes for SCI therapy. Issues like the potential tumorigenesis of iPSCs, timing of transplantation and the high cost versus benefit ratio pose obstacles for the clinical translation of such treatments [43][44][45].

Mesenchymal Stem Cells (MSCs)

Mesenchymal Stem Cells are multipotent cells which can differentiate into various cell types, including adipocytes, chondrocytes, osteoblasts, and vascular smooth muscle cells.
Some evidence suggests potential differentiation into tenocytes. MSCs have been reported to give rise not only to mesenchymal lineages but also to endothelial cells, skeletal and cardiac muscle cells, neural cells, hepatocytes, and epithelial cells. They exhibit differentiation plasticity, with the ability to shift from one differentiation pathway to another under modified external conditions. Lineage priming, a property shared by MSCs, enables expression of genes associated with differentiation pathways even in the absence of induction [46].

Mesenchymal stem cells have antiapoptotic, anti-inflammatory and angiogenic properties. They secrete factors and molecules that promote cell survival and prevent cell death, anti-inflammatory cytokines and other molecules that inhibit the activation and proliferation of immune cells and proangiogenic factors that stimulate endothelial cell proliferation [47].

MSCs gained attention in the search for spinal cord injury treatment, because of their easy isolation, maintaining their regenerative potential after cryopreservation, raising no ethical concerns and minimal or absent immunoreactivity or a reaction versus hosts [48] [49] [50]. They also show remarkable properties of "homing". Attracted by chemotactic substances, such as for example VEGF, HGF and cytokines, they migrate to the lesion site [51].

Mesenchymal stem cells can be isolated from almost all tissues, including amniotic fluid, liver, and heart, but the greatest therapeutic benefits are observed in the transplantation of cells obtained from bone marrow, the umbilical cord and adipose tissue [52].

MSCs: Bone Marrow Mesenchymal Stem Cells

Bone marrow mesenchymal stem cells (BM-MSCs) can be found in the adult bone marrow cavities, around the trabecular bone surface, and in bone marrow sinusoids. They are involved in hematopoiesis and bone regeneration [53]. BM-MSCs can be obtained from various species including humans, rodents, primates, sheep, dogs, cats, and bovines [54] [55] [56] [57]. Trying to identify neuronal phenotypes studies have shown the expression of Nestin in some BM-MSCs, indicating responsiveness to extrinsic signals. While Nestin-positive cells exhibited neuron-like characteristics, they did not display mature neuron electrical features [58].

Numerous preclinical studies have explored the efficacy of BM-MSC transplantation in treating spinal cord injuries across different animal models. Results have been promising, with improvements observed in motor and sensory functions. For instance, in studies involving monkeys and pigs, BM-MSC transplantation led to motor improvements, reduced cavity size, and enhanced sensory evoked potentials [59].

Early trials involving cervical SCI patients have shown limited but promising results. Patients treated with BM-MSCs exhibited slight improvements in motor function in the upper limbs, as well as changes in MRI indicating tissue regeneration [60]. Other clinical studies on chronic and complete cervical SCI patients reported improvements in ASIA scores, AIS grading, and residual urine volume after BM-MSC transplantation [61].

MSCs: Umbilical Cord Mesenchymal Stem Cells

Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) obtained from umbilical cord blood, from the perivascular regions and the umbilical vein [62]. On the neuronal level they seem to have greater benefits than BM-MSCs [63]. In pre-clinical studies, molecular markers and neuron-like characteristics were observed after homogeneous maturation of UC-MSCs. That indicates their potential for inducing positive changes in the damaged spinal cord [64].
Existing trials have reported minor improvements in some patients, such as autonomic restoration and changes in somatosensory evoked potentials, improving motor and sphincteric functions [65] [66].

MSCs: Adipose-Derived Mesenchymal Stem Cells

Adipose-Derived Mesenchymal Stem Cells (AD-MSCs) have a similar morphology to that of UC-MSCs but are characterized by different proliferative capacity and greater availability since adipose tissue contains a higher proportion of stem cells [67]. Studies in animal models revealed positive outcomes such as extensive axon ingrowth, sprouting of raphespinal terminals, and astrocytic processes extension, all indicative of regenerative processes [68]. In clinical studies, intrathecal transplantation of AD-MSCs has shown a slight sensory improvement in the majority of patients. However, concrete motor responses in longitudinal clinical trials are still awaited [69].

Conclusion

Despite encouraging findings in laboratory models and clinical trials involving human subjects, conclusive evidence supporting substantial functional recovery post-spinal cord injury (SCI) through stem cell transplantation is still lacking. The growing volume of human clinical studies over the last decades sparks optimism for significant advancements in enhancing functional outcomes following stem cell transplantation in SCI patients.

Disclosure

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