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Stem Cell Therapies for Functional Recovery After Spinal Cord Injury: Mechanisms, Challenges, and Applications

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Abstract

Context: Spinal cord injury (SCI), a debilitating and catastrophic condition, leads to sensory motor impairments, paralysis, and high mortality. It consists of initial physical insult and secondary injury. Despite much research on SCI treatment, it is still one of the incurable damages because of its complex pathophysiology and limited neuronal regeneration ability. In recent years, stem cell therapy has been a promising and exciting strategy for SCI treatment.

Evidence Acquisition: In this review, the articles published in PubMed, Google Scholar, Science Direct, and Scopus from 2000 to 2022 were collected using keywords such as spinal cord injury, stem cell therapy, neuroprotection, neuroregeneration, neurotrophic factors, anti-inflammatory cytokines, and neural cell death. The articles whose full texts were available and met the inclusion criteria were examined. According to the inclusion criteria, 30 articles were analyzed.

Results: Stem cell therapy can promote neuroplasticity and neuroregeneration in the damaged spinal cord. Grafted cells can reconstruct nerves and create new circuits after SCI. Stem cell transplantation can also replace lost oligodendrocytes, thus promoting axon remyelination. Many neurotrophic factors and anti-inflammatory cytokines are secreted by transplanted stem cells to decrease secondary injury and neural cell death, thus inhibiting the glial scar formation after SCI. Stem cells also have antioxidant, anti-inflammatory, immunomodulatory, and anti-apoptotic effects. Grafted stem cells can block microglial activation and astrocyte reactivity and enhance revascularization.

Conclusions: Stem cells isolated from different tissues can be promising candidates and attractive options for treating the injured spinal cord. Despite remarkable progress in animal studies, cell transplantation's clinical efficacy and adequacy for SCI remain limited and dubitable. Many essential challenges must be considered in translation to the clinic. It is hoped that the invention of new methods and the anti-inflammatory, anti-apoptotic, antioxidant, and neuronal repair properties of stem cells can effectively improve the sensorimotor function of patients with SCI.

Keywords: Spinal Cord Injury, Stem Cell Therapy, Neuroprotection, Neuroregeneration

1. Context:

Spinal cord injury (SCI), as a debilitating and catastrophic condition, leads to sensory motor impairments, paralysis, and high mortality. It consists of initial physical insult and secondary injury. The initial injury is determined by mechanical trauma, tissue necrosis, and damage to spinal neurons and vessels, whereas secondary injury involves inflammatory response, oxidative stress, glutamate-mediated excitotoxicity, edema, and, finally, glial scar formation (1, 2).

Despite much research on SCI treatment, it is still one of the incurable damages because of its complex pathophysiology and limited neuronal regeneration ability. In recent years, stem cell therapy has been a promising and exciting strategy for SCI treatment. Various sources of stem cells are applied for SCI, such as mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs) (3).

Transplanted cells can improve neural functions by replacing damaged or dead cells and the secretory potency of proteins and peptides. Many neurotrophic factors and anti-inflammatory cytokines are secreted by transplanted stem cells to decrease secondary injury and neural cell death, thus inhibiting the glial scar formation after SCI (3, 4). According to the importance of SCI, the current study aimed to investigate the effects of stem cell therapy on functional recovery after this catastrophic condition focusing on their protection mechanisms.

2. Evidence Acquisition

The present study reviews the treatment of SCI with stem cells. Articles were searched from the international databases of PubMed, Google Scholar, Science Direct, and Scopus using keywords such as spinal cord injury, stem cell therapy, neuroprotection, neuroregeneration, neurotrophic factors, anti-inflammatory cytokines, and neural cell death in the period from 2000 to 2022. In this review study, articles were accepted based on the eligibility criteria. The inclusion criteria included studies with relevant keywords and articles with full texts. The exclusion criteria included articles unrelated to the research subject and lacking access to the full text. After checking the full texts, 30 articles were selected and analyzed, and the results were extracted.

3. Results

3.1. Stem Cells and Major Types

Stem cells are undifferentiated cells that can proliferate indefinitely (self-renewal ability) and differentiate into various cell types (potency ability) (5). There are several types of stem cells based on the origin: embryonic stem cells (ESCs), fetal and adult stem cells, and induced pluripotent stem cells (iPSCs) (5).

Embryonic stem cells (ESCs) are derived from the early-stage embryo. These cells are pluripotent that can generate any body cell type (5).

Adult stem cells are multipotent or unipotent. Multipotent stem cells can differentiate into multiple specific cell types. Mesenchymal stem cells and neural stem cells are examples of this cell type. However, unipotent stem cells, such as muscle stem cells, have the potential to produce only one cell type (5). Mesenchymal stem cells (MSCs, or mesenchymal stromal cells) are multipotent cells capable of differentiating into chondrocytes, osteoblasts, adipocytes, and myocytes (4). Mesenchymal stem cells can be isolated from bone marrow and other sources, such as umbilical cord blood, Wharton's jelly, and adipose tissue (6). Neural stem cells (NSCs) can differentiate into neurons and glial cells (2).

Induced pluripotent stem cells (iPSCs) are pluripotent cells originating from non-embryonic somatic cells. The differentiated cells have been converted back to an embryonic state (7).

3.2. Optimal Timing of Stem Cell Transplantation Following Spinal Cord Injury

Free radical formation and inflammatory response significantly contribute to secondary injury cascades following SCI. It occurs immediately following mechanical trauma. In the chronic phase of SCI, the glial scar is formed as a physical and chemical barrier to tissue regeneration. These changes in the spinal cord microenvironment can decrease the survival rate of transplanted cells and affect stem cell differentiation. Therefore, the modification of inflammatory response, oxidative stress, and suppression of glial scar formation must be considered to achieve the maximum recovery of sensorimotor function by stem cell transplantation. Animal studies have shown that the subacute phase of SCI might be the optimal time for stem cell transplantation compared with the acute or chronic phase (8-11). Toxic mediators and inflammatory cytokines are attenuated in the subacute compared with the acute phase (11). However, it is unclear in clinical trials which phase of cell transplantation results in a better outcome (12).

3.3. The Main Goals of Stem Cell Therapy and Its Neuroprotection Mechanisms in Spinal Cord Injury

Stem cell therapy as a regenerative medicine can promote neuroplasticity and neuroregeneration in the damaged spinal cord. Grafted cells can reconstruct nerves and create new circuits after SCI. Stem cell transplantation can also replace lost oligodendrocytes, thus promoting the remyelination process of the demyelinated axons. They can secret trophic factors such as NGF, BDNF, GDNF, and VEGF. These proteins in the nervous system can promote axonal sparing and neuroplasticity and regulate neuronal survival and regeneration (4, 13, 14).

The research showed that transplanted cells could suppress secondary events after SCI through proteins and peptide secretion (3). Stem cells also have antioxidant, anti-inflammatory, immunomodulatory, and anti-apoptotic effects (4, 13, 15). It has been reported that grafted stem cells can block microglial activation and astrocyte reactivity and enhance vascularization (13). Therefore, stem cells isolated from different tissues can be promising candidates and attractive options for treating injured spinal cord (11, 13).

3.4. Stem Cell Therapy and Regenerative Medicine in Spinal Cord Injury

In the recent decade, scientists and researchers have strongly noticed stem cell therapy as a new and attractive therapeutic option for improving the injured spinal cord (16). Neuroprotection of secondary events and neuroregeneration are the main goals of stem cell therapy for SCI. It has been shown that human skin-derived mesenchymal stromal cells can repair damaged tissue and elicit neuronal protection by suppressing immune responses (13). These cells improved locomotor function in the acute phase after SCI (13). Adipose tissue-derived mesenchymal stem cells

have also been shown to treat SCI by replacing lost oligodendrocytes and forming neural plasticity in dogs. The underlying mechanism might be associated with the secretion of molecules that attenuate secondary injury, including anti-inflammatory cytokines and neurotrophins (6).

A study reported that oligodendrogenic neural progenitor cells could improve motor function by facilitating axon remyelination and tissue protection after SCI (2). Also, MSCs derived from different tissue types (umbilical cord and bone marrow) were tested for relieving neuropathic pain following SCI (17). There were no significant differences between the two treatment groups regarding functional recovery and pain relief. Both transplantation groups revealed motor recovery (17).

3.5. Combination of Stem Cell Therapy with Other Treatments

As the pathophysiology of SCI is complex and multifaceted, it seems that combination therapy will have a better outcome. It has been demonstrated that human adipose-derived stem cell transplantation combined with chondroitinase ABC was more effective on motor function than single therapy. These stem cells can secrete neurotrophins and angiogenic growth factors such as NGF, BDNF, GDNF, and VEGF, while chondroitinase ABC (ChABC), as a bacterial enzyme, can wash out glycosaminoglycan (GAG) chains in chondroitin sulfate proteoglycan (CSPG). Chondroitin sulfate proteoglycan is the most abundant molecule in the extracellular matrix and a barrier for axon regeneration. Chondroitin sulfate proteoglycan is a major component of glial scar following SCI (16). Although most transplanted stem cells survived undifferentiated in this research, motor function improvement may be due to neurotrophic and angiogenic factors secretion by grafted stem cells (16).

Another study demonstrated that applying stem cells encapsulated into a biopolymer matrix at the injury site could improve tissue damage and behavioral function. Biopolymer matric as a stem cell delivery system could increase the survival rate of stem cells embedded in it. The researchers found that this novel therapeutic approach may attenuate secondary injury through anti-inflammatory and antioxidative mechanisms and create a balanced microenvironment for neuroregeneration (18). Anti-inflammatory effects may be related to astroglia and microglia inhibition and promoting the M2 macrophage numbers (18).

In a study, a new technology of cell transplantation was introduced. This research demonstrated that the combined application of spheroid cell culture and BDNF transfection increased the therapeutic effects of stem cells, probably via augmented secretion of cytokines and trophic factors (3). In an experimental model of SCI, the new treatment was applied to provide a more suitable microenvironment for the transplantation of neural precursor cells (NPCs, including neural stem and progenitor cells) (19). This study injected self-assembling peptides (SAPs) as an effective biomaterial into the injured tissue and could improve the post-traumatic microenvironment before cell transplantation. This cell scaffold could promote the survival and differentiation of NPCs and reduce glial scar formation (19). Such research may help identify new and effective treatment strategies for SCI.

Many other reports on the efficacy of stem cell transplantation combined with other treatments for SCI have been published. For example, in one study, Requejo-Aguilar et al. indicated that combination therapy of polymer-curcumin conjugate and ependymal progenitor/stem cell (epSPCs) promoted functional recovery through neuroprotection and neuroregeneration creation. Curcumin is a natural and bioactive component in turmeric with anti-inflammatory, antioxidant, and anti-apoptotic effects. Curcumin in the form of a conjugated polymer has improved bioavailability and is a suitable stem cell delivery system (20). This treatment approach may be a novel therapeutic option in SCI clinical trials (20).

17β-estradiol (E2) was applied before Schwann cell transplantation to increase grafted stem cells' survival rate and efficacy after SCI (21). This study showed that combination therapy promoted myelination, neuroregeneration, and functional recovery via increased neuronal survival and reduced microgliosis and astrogliosis (21). The combined transplantation of stem cells for the treatment of SCI has also been evaluated (22, 23).

The combination of stem cell transplantation and gene therapy was also used to optimize SCI treatment (24). The bone marrow stem cells were differentiated into neural-like cells and genetically modified with the GDNF (glial cell line-derived neurotrophic factor) gene. This treatment strategy can be considered one of the future treatment options (24).

In a clinical trial, Yoon et al. found that autologous human bone marrow cell (BMC) transplantation combined with granulocyte macrophage-colony stimulating factor (GM-CSF) administration improved the American Spinal Injury Association (ASIA) Impairment Scale in the neurological examination of sensory and motor functions. This combination therapy promoted functional recovery in the acute and subacute but not chronic phases of SCI. No serious adverse events were observed after treatment, including hemorrhage, infection, cyst, and tumor formation (25).

In another human study, the investigators surveyed umbilical cord blood-derived mononuclear cell (UCB-MNC) or mesenchymal stromal cell (MSC) transplantation

combined with lithium in chronic complete SCI patients. Lithium can be a stimulator for trophic factors secretion by mesenchymal stem cells. The results showed AIS grade improvement in five patients (26). Recently, a clinical trial on 11 patients with complete SCI (grade A) demonstrated that co-treatment with human autologous Schwann cell and bone marrow-derived mesenchymal stem cells during the subacute phase of spinal cord injury could promote sensory and neurological function without severe side effects (27).

3.6. Main Problems of Stem Cell-based Therapy

There are still some critical concerns regarding stem cell therapy that are addressed as follows:

- Ethical issues, particularly with embryonic stem cell (ESC) and neural stem cell (NSC) generation and transplantation

- Safety and technological challenges in the development and transplantation of stem cells

- Immunological problems and immune rejection associated with allogeneic stem cell transplantation

- The risk of tumorigenicity and teratoma formation, particularly by embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs)

Many preclinical studies need to resolve these issues to promote clinical translation (28-30).

Finally, it is necessary to mention that despite remarkable progress in animal studies, cell transplantation's clinical efficacy and adequacy for SCI remain limited and dubitable. There are many essential challenges in the clinical translation of stem cell therapy. The following items must be noted in translation to the clinic: efficacy and adequacy of experimental models, transplantation time (acute, subacute, or chronic phase of SCI), stem cell delivery system (for example, scaffolds seeded with stem cells), the development and application of a suitable biomaterial in medicine, the use of combination therapy approaches for SCI and then the structural and functional evaluation of the damaged spinal cord, genetic manipulation of stem cells, and serious side effects of the grafted cell (12, 18, 24).

Use of a safe and standard procedure for stem cell production, the study of cell transplantation in large and more relevant animal models of preclinical research (such as dogs and non-human primates), and clinical studies with stem cell transplantation in multicenter, randomized, controlled clinical trials are other critical challenges that must be considered in translation to the clinic (18).

4. Conclusions

Despite much research on SCI treatment, it is still one of the incurable injuries because of its complex pathophysiology and limited neuronal regeneration ability. In recent years, stem cell therapy has been a promising strategy for SCI treatment. Transplanted cells can improve neural functions by replacing damaged or dead cells, the secretory potency of cytokines (such as anti-inflammatory cytokines), and many neurotrophic factors that decrease secondary injury and glial scar formation. Despite remarkable progress in animal studies, cell transplantation's clinical efficacy and adequacy for SCI remain limited and dubitable. Many essential challenges must be considered in translation to the clinic.

Footnotes

Authors' Contribution: All the authors had a similar role in collecting articles from relevant databases. Mahmoud Momenzadeh was responsible for presenting the idea of this review article. Zahra Jahanbakhsh wrote the draft of the manuscript. Mitra Yousefpour referenced and revised the manuscript. All authors accept responsibility for the accuracy and correctness of the contents of the final manuscript.

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