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The Action of Hematopoietic Stem Cells in the Pathophysiological Mechanisms of Spinal Cord Injury

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ABSTRACT

Spinal cord injury (SCI) often leads to catastrophic neurological deficits that dramatically reduce a person's quality of life. Stem cells have attracted particular interest as a potential source for cell regeneration therapy after SCI.
The purpose of this study is to review the action of hematopoietic stem cells (HSCs) in the pathophysiological mechanisms of SCI. A literature review was conducted based on the Pubmed internet database, following the PRISMA Guidelines. Article titles were searched with the use of the keywords: ("hematopoietic stem cells" OR "HSCs") AND ("spinal cord injury"). The search included only animal and clinical studies evaluating the action of hematopoietic stem cells in the pathophysiological mechanisms of SCI. Studies published in non-English language, reviews, case reports and study protocols were excluded.
Initially, 39 studies were identified after primary search on Pubmed electronic database. After screening of titles and abstracts, 21 articles were excluded. Among the remaining 18 studies, 9 were rejected as review articles. After checking the references list of the included studies, 13 more studies were added, leaving 22 studies for final analysis. There were 10 clinical studies and 12 animal studies.
The transplanted HSCs may integrate with the host cells in the injured spinal cord tissue, modulating immune and inflammatory reactions. Moreover, they have been associated with axon regeneration and remyelination along with a reduction of glial scar. HSC transplantation has shown promising results in the treatment of SCI, having the potential to repair the injured spinal cord and to enhance functional recovery. However, most studies are experimental and further human studies are needed to fully elucidate the role of HSC in SCI.

KEYWORDS: "spinal cord injury", "hematopoietic stem cells", "transplantation"

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Introduction

Spinal cord injury (SCI) often leads to catastrophic neurological deficits that dramatically reduce a person's quality of life. Surgical fixation and rehabilitation are the only interventions commonly used to improve functional recovery after SCI. Methylprednisolone is the only currently approved pharmaceutical agent and has been used to reduce inflammation in the spinal cord immediately after injury. However, it has limited efficacy and serious side effects, such as gastrointestinal bleeding and increased risk of respiratory infections (1,2). Despite decades of efforts to develop effective methods of management, there is still an urgent need for novel treatment that promotes functional recovery after SCI.

SCI can cause acute damage to the ascending and descending neural pathways and lead to axonotmesis. Immediately after the initial injury, a strong neuroinflammatory response occurs and secondary injury mechanisms are activated in the chronic phases of SCI, leading to cell death and further tissue degeneration. Around the site of injury, cyst formation and growth inhibitory scarring (glial scar) will prevent tissue regeneration (3). For these reasons, stem cells have attracted particular interest as a potential source for cell regeneration therapy after SCI.

Hematopoietic stem cells (HSCs) are a stem cells category, distinguished by a great capacity for self-renewal. They are located in the bone marrow and are responsible for blood formation and the production of all hematopoietic cell lines, such as red blood cells, white blood cells, platelets or lymphocytes. HSCs remain in the marrow at rest and control hemopoiesis by multiplying very rarely, once every 21 weeks. Hematopoietic stem cell progenitors are short-lived hematopoietic cells that produce cell lines for a short period of time (4,5).

Nowadays, HSC transplantation is a modern, established, effective treatment for the treatment of various, severe malignant and genetic hematological diseases. The range of transplantations has expanded dramatically with the use of alternative donors and transplants and as a result, many pediatric patients are treated with the application of this therapeutic procedure. HSCs have been used to treat hematological diseases since 1988, the year of the first successful therapeutic application. Their uses are for the treatment of malignant blood diseases, as well as hereditary hemoglobinopathies and metabolic diseases. In 1988 they were first used to treat aplastic anemia, in 1989 they were used to treat chronic myelogenous leukemia and since 1995 they are considered equivalent to bone marrow stem cells and can have the same therapeutic applications. In 1998 the first autologous HSCs transplantation was performed in a child with a malignant tumor of the nervous system, which even had metastases. In 2007, the first autologous and successful umbilical cord HSCs transplantation was published in a 3-year-old child who developed acute lymphoblastic leukemia and whose family had cryopreserved his stem cells in a private bank (6,7). Today, more than 50.000 HSC transplantations are performed annually worldwide.

There are two types of HSCs transplantations: (a) allogenic in which HSCs are transferred from a healthy individual (donor), genetically compatible or genetically similar, to the patient (recipient); the goal is to replace the patient's abnormal bone marrow with a new, healthy hematopoietic system, (b) autologous in which the HSCs of the patient are removed, collected, processed, frozen, and then, after the administration of chemotherapy, they are thawed and infused. HSCs sources include bone marrow, peripheral blood and umbilical cord blood. CD34 is a marker of human HSCs and human progenitor hematopoietic cells, and all colony-forming activity of human bone marrow cells is found in the CD34+ fraction (8). Studies have shown that HSCs are able to restore hemopoiesis in immunocompromised mice. Their specific ability is based on the CD34+ molecule, which is expressed by these cells. Experiments have also shown that aging HSCs retain their older phenotype after transplantation in young individuals (9).

There are two possible approaches to using stem cells in SCI: Stem cell transplantation at the site of injury and recruitment of neural stem cells of the injured spinal cord (10, 11). The purpose of this study is to review the action of HSCs in the pathophysio-

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logical mechanisms of SCI. A literature review was conducted based on the Pubmed internet database, following the PRISMA Guidelines, with the use of the EndNote X3 software (Thompson Reuters) (12). Article titles were searched with the use of the keywords: ("hematopoietic stem cells" OR "HSCs") AND ("spinal cord injury"). The search included only animal and clinical studies evaluating the action of hematopoietic stem cells in the pathophysiological mechanisms of SCI. Studies published in non-English language, reviews, case reports and study protocols were excluded.

Discussion

Initially, 39 studies were identified after primary search on Pubmed electronic database. After screening of titles and abstracts, 21 articles were excluded. Among the remaining 18 studies, 9 were rejected as review articles (figure 1). After checking the references list of the included studies, 13 more studies were added, leaving 22 studies for final analysis. There were 10 clinical studies (13-22) and 12 animal studies (23-34).

Animal Studies

Recently, there is an emerging number of animal studies focusing on the application of HSCs in the treatment of SCI. In 2017, an animal study by Xiong et al analyzed the results of the injection of HSCs into SCI rats and observed that HSCs may enhance the formation of 5-HT (+) fibers and oligodendrocytes in the spinal cord, attenuate astrocyte hyperplasia, and upregulate neurotrophins-3 (NT-3) mediated mitogen-activated protein kinase kinase (MEK-1) expression, thereby improving motor and sensory recovery in SCI rats (25). Koda et al compared the results of HSC and BMSC transplantation in SCI mice. One week following SCI, HSCs, BMSCs or saline were transplanted into the site of SCI. No significant difference was recorded in the motor and sensory scores among studied groups. Injected HSCs and BMSCs survived in the site of injury. Furthermore, injected HSCs expressed a neural lineage marker, whereas BMSCs kept their original phenotype. Authors concluded that HSCs and BMSCs have the capacity to restore the injured spinal cord and to enhance functional recovery of hind limb motor function (23).

In 2004, Zhao et al demonstrated that intraspinal injection of umbilical cord–derived HSCs into the spinal cord improved functional outcome and survival rate in a rat spinal cord hemisection model (28). The same year, Koshizuka et al directly injected HSCs into the spinal cord of mice 1 week after SCI and checked hindlimb motor function once per week for 5 weeks after injection. An important improvement in the functional results of mice transplanted with HSCs was observed in comparison with the control group. Transplanted HSCs were found to survive 5 weeks after injection and expressed specific biomarkers for astrocytes, oligodendrocytes and neural precursors, but not for neurons. Authors concluded that HSCs transplantation is a helpful method for the treatment of SCI (24).

In another animal study including 40 SCI rats, intrathecal transplantation of umbilical cord HSCs was found to improve spinal cord function, when delivered 30 min after experimental SCI (31). Dasari et al showed that umbilical cord HSCs, when injected into the spinal cord 7 days of 52 adult male rats after SCI, survive for at least 2 weeks, differentiate into oligodendrocytes and neurons, and facilitating functional recovery after moderate SCI, with a beneficial effect in the reversal of the behavioral effects of SCI (32). In another experimental study, the same authors observed that umbilical cord HSCs when transplanted in the SCI site 1 week after injury, may inhibit neuronal apoptosis during the repair of injured spinal cord (33).

Nishio et al reported that transplantation of CD34+ umbilical cord–derived HSCs used in SCI rats improved hind-limb motor function, and enhanced the regeneration of spinal cord tissue and axons. Transplanted HSCs disappeared 5 weeks after transplanation (26). Recently, according to Yeng et al, the neuroprotective effects of conditioned medium from cultured human CD34+ cells are similar to those of human CD34+ cells and the conditioned medium was found to augment the neuroprotective effects of estradiol in SCI rats (27). In an experimental comparative study, Cao et al evaluated the results of combined laminectomy with the

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administration of umbilical cord derived CD34(+) cells in SCI rats. Authors concluded that CD34(+) cell transplantation may reverse the SCI-induced spinal cord infarction and apoptosis and hindlimb dysfunction by triggering the production of both vascular endothelial growth factor (VEGF) and glial cell line-derived neurotrophic factor (GDNF) in SCI rats (29). A similar randomized comparative study by Ning et al, observed that transplantation of umbilical cord derived CD34(+) during the acute phase of SCI may enhance the functional recovery better than during the subacute phase after SCI by increasing blood vessel density. Transplanted HSCs were found to survive at least 3 weeks after injection, but did not differentiate into neural cells (30). An animal study by Takahashi et al, found that intraspinal injection of granulocyte colony-stimulating factor (G-CSF) - mobilized peripheral blood derived-CD34(+) cells enhanced angiogenesis, serotonergic fiber regeneration/sparing, and preservation of myelin, resulting in improved hindlimb function after SCI (34).

Clinical studies

In a prospective study, published in 2012, Frolov and Bryukhovetskiy transplanted intrathecally CD34+ HSCs in 20 chronic SCI patients and used regular neurophysiologic examination for at least 1 year to assess neurological recovery. In 3 patients the initially absent short-latency somatosensory evoked potentials were restored. In 4 patients, the N20P23 interpeak amplitude elicited by median nerve stimulation was increased. In 2 patients, the P38 latency in somatosensory evoked potentials elicited by tibial nerve stimulation was decreased. In 3 patients, the motor evoked potentials appeared. Authors commented that the mixed results of HSCs transplantation are due to the variety of spinal cord lesions and the different pathways involved. The results of the study demonstrate the ability of HSCs to install and spread within the spinal cord, participating in the neurological recovery process (16).

An Iraqian study published in 2012 enrolled 277 SCI patients. Peripheral blood-derived HSCs were injected into the spinal cord, 1-4 times within 6-8 weeks. 56.7% of patients showed no neurological improvement, while the rest of the patients (43.3%) experienced clinical improvement after 4 weeks. Transient backache was recorded in 90% of cases (17). Thakkar et al, in 2016, in a prospective single arm open-labeled clinical trial, evaluated the therapeutic combined infusion of HSCs and autologous adipose tissue-derived mesenchymal stem cell differentiated neuronal cells in the spinal cord of 10 SCI patients. After a 3-year follow-up, variable clinical improvements were observed. All patients mentioned subjective crude pain sensation at 15 days after treatment. Sixty per cent of patients reported crude touch sensation 30 days after treatment, followed by fine touch sensation and deep pain sensation 3 months after treatment up to 3-4 levels below SCI. At 3 months after infusion, all patients could stand with aid, with a gradual increase of the duration of standing. At 8 months, 80% of patients could walk for at least 1 hour without help. At 3-years follow-up, in half of the patients, the control of bladder and bowel was significantly improved. No complications or side effects were observed (18).

Al-Zoubi et al, in a prospective cohort study, evaluated the efficacy of transplantation of CD34+ HSCs in the spinal canal of 19 patients with complete thoracic SCI. At a 5-year follow-up, 7 patients had improvement in segmental sensation, 2 patients had improvement in motor function, showing improved strength of abdominal and hip muscles, allowing them to walk with aids. No side effects were recorded (19). In 2015, Bryukhovetskiy et al conducted an open parallel controlled trial including 202 SCI patients and 20 matched controls. A combination of HSCs and hematopoietic progenitor cells was administered intrathecally every 3 months for 3-5 years. At the 3 years follow-up, the efficacy of the combined transplantation was 57.4%. No clinical improvement was observed in 42.6% of cases. Half of the patients experienced a degree of motor recovery, initiated after the first transplantation. In 47.7% of patients, bladder function was improved. Improvement of neurological symptoms was observed in 56.9% of cases. No complications or severe side effects were recorded. Authors concluded that the method is safe, effective and considerably improves the life quality of SCI patients (14).

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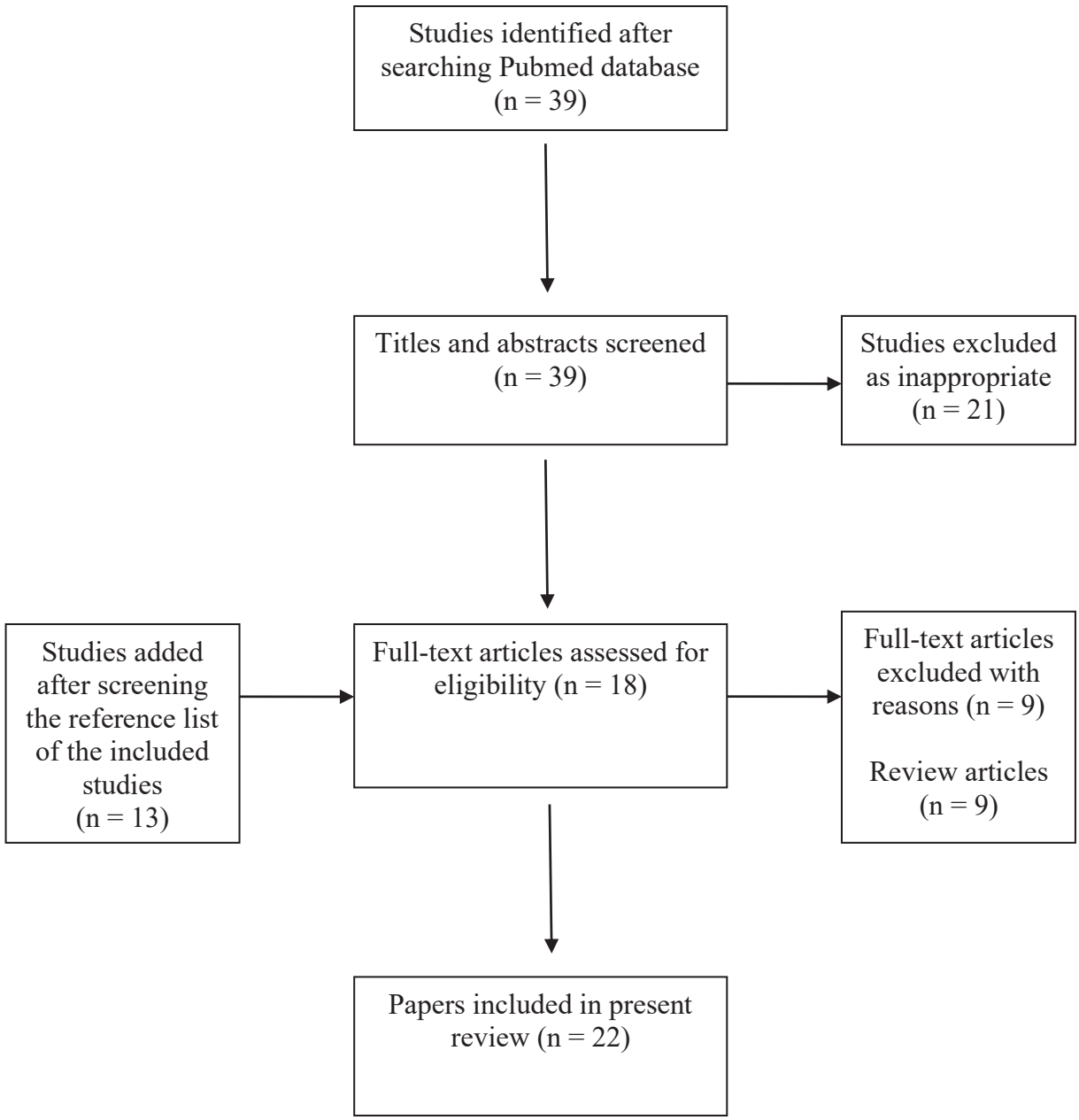

Figure 1. *Study flowchart*

In 2017, Ammar et al published a study including 4 SCI patients that underwent reconstruction of the spinal cord using a combination of autologous HSCs and platelet-rich protein (PRP) that served as a scaffold for the HSCs. Postoperatively, patients were checked clinically with regular electromyograms and MRIs. After a 2-3 years follow-up, one patient demonstrated motor and objective sensory improvement, two others reported subjective sensory improvement, and the fourth patient remained without any improvement. No complications or clinical deterioration was recorded. All the insert-

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ed biological scaffolds remained intact, as shown in MRI studies (13). Another study by Deda et al assessed 9 patients with chronic (more than 6 months) complete SCI, ASIA grade A, who were treated with autologous bone marrow-derived HSCs transplantation, during laminectomy. With a 3-weeks follow-up, all patients experienced motor and sensory improvement (ASIA grade B or C). No complications or severe side effects were recorded (15). A prospective, non-randomized clinical study examined the effect of CD34+ cells infusion on 39 patients (28 males and 11 females) with complete cervical and thoracic SCI. After a - 2.5 years follow-up, neurophysiologic examination revealed that 67% of the patients showed recovery of somatosensory evoked potentials in response to peripheral stimuli. This finding may be explained by the HSC-induced formation of new synapses between neurons or by new myelination of glial cells. The rate of complications was 10.2% including one case of pneumothorax and 3 allergic reactions (21). In another case series by Geffner et al, CD34+ cells were administered in 8 SCI patients either into the spinal cord or intravenously. Authors observed morphological changes in spinal cord, as depicted in MRI studies. CD34+ cells transplantation improved the quality of life of all patients, without any severe adverse events (20). Callera and de Melo, in a comparative study, found that autologous bone marrow CD34+ cells labeled with magnetic nanoparticles that were injected into the spinal cord migrated into the injured site in 16 patients with chronic SCI (22) .

The exact mechanism of functional recovery enhancement induced by HSC transplantation has not yet been clarified. HSCs may secrete neurotrophic growth factors, such as angiopoietin-1, which can enhance restoration of the spinal cord and improve functional outcome. (35,36). The transplanted HSCs may integrate with the host cells in the injured spinal cord tissue, modulating immune and inflammatory reactions. Moreover, they have been associated with axon regeneration and remyelination along with a reduction of glial scar (37).

HSC transplantation has several advantages. They can be easily obtained from bone marrow from animals and humans. HSCs can be transplanted without cultivation as optimal timing for HSC transplantation in SCI is limited to the first 1–2 weeks after SCI (38,39). The disadvantages include a difficulty in acquiring an adequate number of HSCs, as they constitute less than 1% of bone marrow cells in the adult human, and ex-vivo expansion of HSCs has not yet been established. Alternatively, umbilical cord blood may be used as a source of HSCs. These HSCs can be used for cell therapy for SCI, as they are abundant, immature, with low rate of immunologic rejection and with a potential application for treatment of central nervous system diseases (40).

Conclusions

HSC transplantation has shown promising results in the treatment of SCI, having the potential to repair the injured spinal cord and to enhance functional recovery. However, most studies are experimental and the clinical application of HSC transplantation in SCI needs further high-quality clinical trials. It seems that the combination of HSC transplantation with tissue engineering scaffolds, local drug administration and postoperative physical and occupational therapy may help SCI patients regain their normal life. Further human studies are needed to fully elucidate the role of HSC in SCI.

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