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Review Article

Bone Marrow Stromal Cell Therapy for Spinal Cord Repair

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Abstract

Spinal cord injury is a devastating condition, for which to date no cure exists. Following damage to the spinal cord, an extensive pathophysiological response creates a hostile environment including inflammation, ischemia, oxidative stress and glial scar formation, resulting in secondary degeneration of tissue and inhibition of axonal growth. Potential repair strategies may therefore need to include interventions that elicit neuroprotection, angiogenesis, scar reduction and/or immune modulation. Cell therapy is a promising strategy to repair the injured spinal cord. Transplanted cells may replace lost or damaged tissue and remyelinate axons or exert repair-supporting paracrine effects. Bone marrow stromal cells (BMSCs) are being extensively studied for their repair-promoting potential in rodent models of spinal cord injury. These cells secrete trophic, angiogenic, and immune modulatory factors that are believed to reduce secondary degeneration and improve functional recovery. Current investigations of BMSC therapy focus on unraveling mechanisms of repair, improving their survival, and optimizing their efficacy through gene therapy, combination strategies, and promotion of cell survival.

Keywords: Spinal cord injury; Bone marrow stromal cells; Cell therapy; Neuroprotection; Trophic factors

Introduction

Traumatic spinal cord injury resulting in functional impairments affects an estimated 500.000 people in the United States and Europe alone and the annual incidence is estimated to be between sixteen per million in Western Europe and forty per million in the United States [1]. The most prevalent causes of traumatic spinal cord injury include traffic accidents, falls, sport injuries, and violence [2]. Non-traumatic causes include tumor compression and infection. Males are affected more than females (4:1) and the average age at the time of injury is 42.6 years [2]. Cushing in 1927 reported spinal cord injury mortality rates of 80 % in the first week, with infections from bed sores and catheterization being leading causes of death [3]. Since then the mortality rate after an injury to the spinal cord has greatly improved due to improved critical care management; however, it is still significantly decreased and estimated to be 70% of normal for complete tetraplegics, 84% for complete paraplegia and at least 92% for incomplete lesions for persons surviving the first 18 months after injury (>90%) [4], with pneumonia and septicemia being the main causes of death [2]. Although the life expectance has much improved, the prognosis for the neurological deficits typically seen after spinal cord injury has remained unchanged. Endogenous recovery is absent in most patients and treatments that effectively reverse the functional deficits below the level of injury have not been discovered yet. Most spinal cord injured patients therefore have to live with permanent paralysis. Life time health care costs vary between one and five million dollars per patient, making it one of the most expensive conditions to treat [2].

Pathophysiology

The initial impact of a spinal cord injury results in immediate rupturing of blood vessels and membranes of neuronal cell bodies and axons, resulting in acute partial or complete motor, sensory, and autonomous dysfunction below the level of injury [5]. The impact further sets off a series of pathophysiological events causing progressive secondary damage which continues for days to months after injury. The initial inflammatory response includes complement activation and neutrophil influx, resulting in edema at the injury site and formation of reactive oxygen species. Within the first days after injury, this neutrophil invasion is replaced by a massive influx of monocytes/macrophages and activation of resident microglia, perpetuating for months after injury [6]. Although these cells may have some beneficial effects, they cause additional damage by exacerbating oxidative stress and membrane damage [7]. Vascular damage, in addition to causing hemorrhaging and contributing to inflammation, results in a shortage of oxygen and nutrients, causing further, ischemic, cell death. Although an endogenous angiogenic response is seen between three and seven days after injury [8], these newly formed blood vessels are often not (yet) functional and lack a functional blood-spinal cord barrier [9]. Meanwhile, invading fibroblasts and resident activated astrocytes form scar tissue which contains axon growth inhibitory molecules, including proteoglycans [10, 11]. Apoptosis continues to take place for months and the ensuing tissue loss results in the formation of fluid-filled cysts. In addition, axons that were spared during the initial impact may undergo progressive degeneration, possibly due to loss of supportive vascular and glial cells and injury-induced mechanism within the neuron [5]. Although sprouting of spared axons does occur, regenerative efforts are minimal and do not lead to significant functional recovery [11]. Understanding the pathophysiology after spinal cord injury is the basis for the development of rational treatments for spinal cord repair.

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Current treatments

Current treatments after spinal cord injury focus on prevention of further damage by pre-hospital spinal immobilization, decompressive and stabilizing surgery, and maintaining or augmenting blood pressure to protect perfusion to the spinal cord. Rehabilitation should start soon after stabilization and ideally constitutes a multi-disciplinary approach including physical and occupational therapy, management of bowel/bladder dysfunction and pressure ulcers, speech therapy for assistance with communication and swallowing and psychological and social guidance of the patient and his or her family. Physical therapy has not been standardized and may vary from passive movements to intense locomotor training using robotic devices [12]. Physical therapy is crucial for maintaining cardiovascular health, preventing diabetes and obesity, limiting muscle atrophy and contractures and preventing osteoporosis [13, 14]. However, there is currently no evidence that neurological deficits can be improved by any of these exercise regimens. Further studies are crucial to determine the proper timing and intensity of rehabilitative strategies to elicit functional recovery. Currently, there are a number of clinical trials being conducted, assessing and comparing the benefits of automated locomotor training, treadmill training, aquatic exercise therapy and other exercise regiments.

A number of pharmacological agents have shown promise in pre-clinical studies and some have been studied in randomized controlled blinded trials. Methylprednisolone, a corticosteroid which may at high dose decrease the inflammatory response after injury, was routinely used in the acute phase of spinal cord injury after the National Acute Spinal Cord Injury Study II (NASCIS II; a multi-center randomized controlled double-blinded clinical trial) showed that very high doses (bolus of 30 mg/kg followed by 5.4 mg/kg/h for 23 hours) administered within 8 hours after spinal cord injury showed significant improvements in motor and sensory function at 6 months post-injury, without harmful side effects [15]. A follow-up study (NASCIS III), comparing 24 hour treatment to 48 hour treatment, recommended 24 hour maintenance for patients treated within three hours of injury and 48 hour maintenance for patients treated between 3 and 8 hours [16]. However, careful re-evaluation of the methodology and statistics used in these studies, meta-analyses including smaller trials of methylprednisolone's effect, and reports on harmful side effects of methylprednisolone has led to the conclusion that there is no evidence to support its use [17, 18]. Similarly, clinical trials of other pharmacological agents, including GM-1 ganglioside, tirilazad mesylate and naloxone has not led to convincing evidence supporting the routine use of these drugs for acute spinal cord injury [19]. Currently, a phase III clinical trial is underway in Canada testing the effect of the neuroprotective antibiotic Minocycline on motor function recovery after acute spinal cord injury. In a previous phase II clinical trial Minocycline was shown to be safe, feasible and showed a tendency towards improved functional recovery [20]. The results of the current phase III trial are expected in 2018. Ongoing efforts are being made to discover and test pharmacological agents that have potential beneficial effects on neuronal tissue and functional recovery.

Stem cell therapy

A promising strategy for spinal cord repair is cell therapy. Cellular transplants have been widely studied in spinal cord injury model systems over the past decades with the aim to replace lost or damaged cells, provide trophic support and/or provide a substrate for axonal growth. In particular, stem cells have shown promise as a spinal cord injury therapeutic. Different types of stem cells can be used for spinal cord repair; each type with its specific advantages and disadvantages. Embryonic and fetal stem cells have the advantage of the potential to differentiate into almost any cell type and could therefore be used to replace damaged and lost neural cells. Disadvantages of these cells include ethical considerations regarding cell harvest and the risk of tumor formation as a result of uninhibited proliferation. Adult stem cells or somatic stem cells are a second type of stem cells that are derived from tissue in the adult body, including neural stem cells from the brain, mesenchymal stem cells from adipose tissue, muscles or bone marrow, and epidermal neural crest stem cells from hair follicles. These cells have less differentiation capacity but are also less tumorigenic. Recently, a third type of stem cell has been developed that circumvents the ethical problems of using embryonic and fetal stem cells — the induced pluripotent stem (iPS) cell, generated from an adult somatic cell by introducing transcriptional factors whose ectopic expression reprograms the cell into a pluripotent cell [21]. The groundbreaking discovery 'that mature cells can be reprogrammed to become pluripotent' has earned Yamanaka the Nobel Prize in Physiology or Medicine 2012. The prize was shared with John B. Gurdon who in 1962 used an enucleated oocyte into which the nucleus of an adult cell was transferred to create a stem cell capable of forming a blastula and eventually a tadpole [22]. Although there are still technical issues that will need to be resolved with the use of iPS, including suppressing tumorigenicity and optimizing differentiation capacity, the discovery of generating stem cells from somatic cells opens exciting new avenues in the field of regenerative medicine [23].

In general, considering the pathophysiology after spinal cord injury, with inflammatory and ischemic processes playing a prominent role in secondary tissue loss, mere replacement of lost or damaged neural cells will likely not be sufficient to restore function. Firstly, a transplanted cell would need to survive in the hostile, ischemic, inflamed environment that constitutes the injury site. Secondly, in the case of replacing a neuron, the new neuron would have to extend its axon across the glial scar, which expresses axon growth inhibitory glycoproteins and surrounds one or more fluid-filled cysts. Thirdly, the axon would need to form synapses that are conducive to functional restoration. Aberrant connections might actually worsen outcome. Sprouting of endogenous sensory axons was shown to contribute to allodynia and hyperalgesia after spinal cord injury [24,25]. In the process of these regenerative efforts the transplanted cells would need to be protected from the neurodegenerative fate of their endogenous counterparts. A multifaceted approach taking into account neuroprotection, blood vessel protection/angiogenesis, and scar reduction/prevention will likely be needed to achieve replacement of lost neural cells by transplanted stem cells.

In previous studies it was shown that stem cells secrete numerous repair-supporting molecules and that their main effect may in fact be to elicit neuroprotective and trophic activities, thereby promoting survival and proliferation of neuronal and endothelial cells and reducing secondary degeneration. One widely studied adult stem cell is the bone marrow-derived mesenchymal stem cell or bone marrow stromal cell (BMSC), on which the remainder of this review will focus.

Bone marrow stromal cell therapy

BMSCs were shown to have beneficial effects on histological and functional outcomes after spinal cord injury in rodent models [26-29]. BMSCs are relatively easy to harvest from adult bone marrow and can be cultured quickly in defined growth medium. The efficacy of BMSCs is thought to be due to the paracrine actions of secreted factors. BSMCs secrete a variety of growth factors and cytokines that can be grouped into three repair-promoting categories. The first group includes molecules that affect blood vessel survival, angiogenesis and stabilization, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and angiopoietin-1 (ANG-1) [30, 31]. Transplants of BMSCs were shown to result in increased blood vessel density near the injury/transplant suggesting that BMSC-mediated angiogenesis is involved in its neuroprotective actions [26]. The second group includes molecules that affect cell survival, including brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and ß-fibroblast growth factor (ß-FGF) [32, 33]. BDNF has been used to enhance the therapeutic potential of BMSCs; genetic modification of BMSCs to hypersecrete BDNF enhanced axonal regeneration in a complete transection model [34]. This study nicely exemplified that BMSCs can be used as effective vehicles for delivery of growth factors. However, the observed enhanced axonal sprouting was not associated with improved functional recovery in this study. A specific repair-related event may be affected by many different trophic factors and, conversely, a particular trophic factor may affect multiple events. It is therefore important to acquire thorough understanding of the role(s) of a particular repair-supporting factor, including the benefits and detriments, before approaches can be developed to enhance BMSC-based spinal cord repair. The third group includes molecules that affect the immune response, including interleukin-10 (IL-10) and transforming growth factor ß-1 (TGF-ß1). The inflammatory response plays a dual role in spinal cord injury. After the initial impact, a massive influx and proliferation of macrophages is evident. These macrophages clear cellular debris and reorganize tissue at the injury site, but in doing so they secrete molecules that increase oxidative stress and worsen secondary tissue degeneration. There are two subsets of macrophages: M1 macrophages with mainly pro-inflammatory, anti-regenerative effects and M2 macrophages with mainly anti-inflammatory, pro-regenerative effects [7]. Within the setting of this complex inflammatory response, the role of immune modulatory factors secreted by BMSCs remains to be elucidated.

BMSC survival

Survival of BMSCs in the damaged spinal cord is poor and this limits their repair efficacy. The death of transplanted BMSCs likely depends on the severity of the injury. It was shown using an adult rat model of a clinically relevant contusion injury of the spinal cord that at one week after transplantation, about twenty percent of the BMSCs survive [35, 36]. Different factors may contribute to this poor BMSC survival, including phagocytosis by the abundantly present macrophages, lack of oxygen and nutrients by ruptured blood vessels, and the presence of reactive oxygen species and other cytotoxic molecules at the injury site. Transplanting the cells in the novel reverse thermal gel poly (ethylene glycol) -poly(serinol hexamethyleneurethane), or ESHU, which has anti-oxidative properties, increases short-term but not long term survival [36]. A likely contributor to this improved BMSC survival was the anti-oxidative ability of the poly-urethane group of ESHU. Increased survival was shown to be associated with increased tissue sparing and improved motor and sensorimotor recovery, stressing the relevance of developing strategies to increase the survival of cellular transplants. Timing of BMSC transplantation also influences survival. Nandoe Tewarie et al. showed that acute (15 minutes post-injury) and subacute (3 days after injury) transplantation of cells results in better survival than late transplantation (7 days post-injury or 28 days post-injury) and increased survival was associated with increased tissue sparing [37].

Factors determining outcome

Interestingly, investigations of BMSC transplants in spinal cord injury have led to different and at times conflicting conclusions. Many but not all groups working with BMSCs reported anatomical or functional improvements after BMSC transplantation in the injured spinal cord and some described axonal regeneration in the injured spinal cord following BMSC transplantation. Many different aspects can influence the effects of BMSCs on repair in models of spinal cord injury. Firstly, the age of BMSCs affects their genetic expression profile, including expression of genes involved in neural repair. Characterization of the gene expression profiles of BMSCs that were passaged three (P3) or fourteen (P14) times in vitro revealed a decrease in plasticity and repair aptitude of long-term cultured BMSCs [38]. In addition, the age of the rat from which the BMSCs are harvested affect BMSC plasticity and their proliferative life span. BMSCs from younger rats have higher telomerase activity and higher expression of Sox-2 and Nanog, increasing their proliferative life span and cell plasticity, respectively [39, 40]. Also, human bone marrow stromal cells exhibit donor variations in secretion patterns of growth factors and cytokines, affecting axon growth and functional recovery in rat spinal cord injury [41]. Clearly, determination and standardization of the optimal BMSC age and donor lot is necessary to validly compare studies and move forward with BMSC therapy research.

Another major factor that has to be taken into account while determining the ability of BMSC transplantation to achieve anatomical repair and functional recovery after spinal cord injury, is the model system used. The strain and gender of the rats used affect the immune response to the transplanted BMSCs. Female rats are often preferred because their short urethra makes manual bladder expression more practical, while their more gentile temperament makes handling easier. Sprague Dawley rats are a commonly used outbred strain, resulting in greater surgery survival rates and less complications than more inbred strains like Fischer rats. However, one has to keep in mind that allogeneic transplantations in Sprague Dawley rats could result in different immune responses than in more inbred strains. Different injury devices, injury types and injury levels used result in different baseline functional deficits. Future research needs to determine which types of injury model best predicts functional recovery in humans, and the site, dose and timing of BMSC injection influence cell survival and cell dynamics. Differences in any of these factors can impact the observed outcome. A golden standard model system for testing cellular transplants for spinal cord injury does not exist. On the other hand, there is a high degree of variation between humans

and having differences between models of spinal cord injury may in fact support our understanding of the potential of BMSC-based spinal cord repair.

Although the rat contusion model of spinal cord injury shows considerable anatomical similarities to human spinal cord injury, and is generally considered to be a suitable model system, there are limitations that affect the interpretation of the repair effects of BMSCs in light of their potential for human spinal cord repair. Firstly, rats show some degree of functional recovery even in the complete absence of supraspinal input, likely due to the presence of a locomotor central pattern generator (CPG) in the lumbar spinal cord segments. Within days after injury, rats will start to show hindlimb joint movements, followed by stepping movements, and, depending on the severity of the injury, weight supported stepping. Reorganization of the CPG is believed to underlie this functional recovery. Humans do not seem to reorganize their lumbar spinal neurons in a way that leads to functional recovery, even though a lumbar CPG is present. Rats are quadrupeds and following awakening from anesthesia after a spinal cord injury, they begin to move around using their forelimbs while dragging their hind limbs. This constant sensory input to the hind limbs may positively affect functional recovery. Indeed, a recent study shows that hind limb immobilization and hind limb stretching therapy in rats hinders the functional recovery of spinal cord injured rats [42]. Treatments tested in rats that improve functional repair, might do so by positively affecting spinal cord reorganization below the level of injury. Humans might be more dependent on supraspinal input for effective functional recovery. The widely used BBB locomotor recovery scale used in rats may not adequately reflect these differences. In the 21-point BBB scale small changes in tissue can be correlated to changes on the scale [43]. In humans, no scale exists in which the extent of tissue damage/sparing can be correlated with a functional rating scale. Although it seems plausible that neuroprotective interventions that are so closely correlated to functional recovery in rats would also be beneficial for humans, no such evidence exists to date.

From bench to bedside

The first clinical trial using human stem cells for spinal cord injury was approved in 2009 by the United States Food and Drug Administration (FDA). In this Phase I trial, oligodendrocyte progenitor cells derived from human ESCs were safely transplanted into five severe spinal cord injured patients. In November 2011 the trial was discontinued. Another Phase I/II trial by StemCells Inc using human CNS stem cells for spinal cord injury is currently underway in Switzerland and Canada and has recently (October 2013) been approved by the FDA. Another cell type that has recently been FDA approved for a clinical trial is the Schwann cell. In rodent models, transplantation of Schwann cells lead to axonal growth and myelination, neuronal tissue loss, and improved motor function recovery after spinal cord injury. Several other clinical trials are in or have completed phase I/II of safety, but large trials of efficacy of (stem) cell therapy for spinal cord injury are still lacking.

Understanding the factors underlying the observed differences in recovery between rats and humans as well as gaining insight in the mechanisms of action of proposed treatments will help us predict which (combination of) therapies may restore function in humans. Conversely, data from the few spinal cord injured patients injected with cellular transplants so far, both from the discontinued Geron trial, as well as from the ongoing StemCell trial may provide us with insights regarding the questions we need to focus on in the laboratory. However, caution is warranted when efforts to translate therapies into the clinic are taken too prematurely, since lack of efficacy in incompletely understood treatments, might unduly discourage patients, the scientific community as well as funding agencies, and decrease the progress of basic research.

Combination strategies

Clearly, BMSCs or any stem cell by itself will not provide the 'silver bullet' for restoring functional repair after spinal cord injury. The neuroprotective properties of these cells will have to be combined with regenerative and rehabilitative strategies to regain function after paralysis. Combining BMSC therapy with motor training has not yet been proven effective [44], but combination with Schwann cells [45], platelet-rich plasma [46] or Rho-kinase inhibitor Fusadil [47] may result in some additive effects. A recent study by Van Den Brand et al. combined three treatments, a monoamine agonist, epidural electrical stimulation and neurorehabilitation within a robotic harness, to considerably improve walking after spinal cord injury in a rat model [48]. However, this study used bipedal locomotion to assess and train recovery, making inferences about supraspinal control difficult, since vertical positioning can influence the central pattern generator in rats [49, 50].

Conclusion

BMSC transplantation is a promising cell-based strategy to promote repair of the injured spinal cord. The knowledge we gain from studying BMSC transplants within spinal cord injury models, provides valuable insights into cell-based treatments for central nervous system disorders that can one day be translated into the clinic providing treatments to improve the quality of life of spinal cord injured patients.

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