Review

Delving into the recent advancements of spinal cord injury treatment: a review of recent progress

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Abstract

Spinal cord injury (SCI) research is a very complex field lending to why reviews of SCI literatures can be beneficial to current and future researchers. This review focuses on recent articles regarding potential modalities for the treatment and management of SCI. The modalities were broken down into four categories: neuroprotection-pharmacologic, neuroprotection-non-pharmacologic, neuroregeneration-pharmacologic, neuroregeneration-non-pharmacologic. Peer-reviewed articles were found using PubMed with search terms: "spinal cord injury", "spinal cord injury neuroregeneration", "olfactory ensheathing cells spinal cord injury", "rho-rock inhibitors spinal cord injury", "neural stem cell", "scaffold", "neural stem cell transplantation", "exosomes and SCI", "epidural stimulation SCI", "brain-computer interfaces and SCI". Most recent articles spanning two years were chosen for their relevance to the categories of SCI management and treatment. There has been a plethora of pre-clinical studies completed with their results being difficult to replicate in clinical studies. Therefore, scientists should focus on understanding and applying the results of previous research to develop more efficacious preclinical studies and clinical trials.

Key Words: brain-computer interface; epidural stimulation; exosomes; neuroprotection; neuroregeneration; scaffolds; spinal cord injury management; stem cells; transplantation

Introduction

Spinal cord injury (SCI) can result in both sensory and motor functional deficits lending to why this type of injury can be both mentally and physically debilitating to the people it affects. The most common causes of SCI in the United States include car accidents, falls, and gunshots with the majority of victims being middle aged men (Mehdar et al., 2019; Xiao et al., 2019). As the population of the United States increases every year, SCI becomes more prevalent. In 2018, it was believed approximately 288,000 people in the United States were living with SCI. It is now estimated that as of mid-2020 there are 294,000 people in the United States living with SCI (National Spinal Cord Injury Statistical Center, 2020). Increasing prevalence of SCI not only affects the number of victims, but also puts further stress on the healthcare system. The average lifetime cost of rehabilitation for SCI victims can exceed $750,000, leading to a total estimated 6 billion dollars in annual expenditures for SCI in the US (Xiao et al., 2019). As of mid-2020 there are no effective treatments for SCI and the burden it posts on humanity and healthcare increases each year.

This review focuses on recent articles regarding potential modalities for the treatment and management of SCI. The modalities have been split into two categories, neuroprotection and neuroregeneration, and then further divided into pharmacologic and non-pharmacologic aspects of each category. It is important to note that all of the modalities mentioned have been studied recently and therefore more data need to be collected so each potential treatment can be better understood.

Database Search Strategy

Peer-reviewed articles were found using PubMed with search terms: "spinal cord injury", "spinal cord injury neuroregeneration", "olfactory ensheathing cells spinal cord injury", "rho-rock inhibitors spinal cord injury", "neural stem cell", "scaffold", "neural stem cell transplantation", "exosomes and SCI", "epidural stimulation SCI", "brain-computer interfaces and SCI". Articles were chosen based on their date of publication as well as their relevance to the categories of SCI management and treatment (**Figure 1**).

Primary *versus* Secondary Spinal Cord Injury

It is a common misconception that the initial trauma to the spinal cord is the only aspect contributing to the debilitating motor and sensory losses one sees in SCI. The body's response to SCI can play just as big of a role when looking at SCI outcomes.

Primary SCI is defined as the physical force(s) that cause the SCI including: compression, laceration, shearing, and stretching (Ahuja et al., 2017).

Secondary SCI is defined as the tissue injury occurring after the primary SCI (Ahuja et al., 2017). An elementary example would be inflammation. Inflammation results from the migration of microglia (macrophages), lymphocytes, and neutrophils to the site of injury, possibly disrupting the blood spinal cord barrier (Ahuja et al., 2017; Courtine and Sofroniew, 2019). These cells in turn release TNF-alpha and various other cytokines and interleukins contributing to the deleterious

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Review

PubMed search terms: "spinal cord injury", "spinal cord injury neuroregeneration", "olfactory ensheathing cells spinal cord injury", "rho-rock inhibitors spinal cord injury", "neural stem cell", "scaffold", "neural stem cell transplantation", "exosomes and SCI", "epidural stimulation SCI", "brain-computer interfaces and SCI"

Articles found between years 2019–2020: included

Articles found outside years 2019–2020: excluded

754 articles found

Articles only addressing a topic specific to the search criteria: e.g. SCI, neural stem cells, and exosomes

Articles addressing multiple topics including the search criteria: e.g., SCI, neural stem cells, and Alzheimer's disease
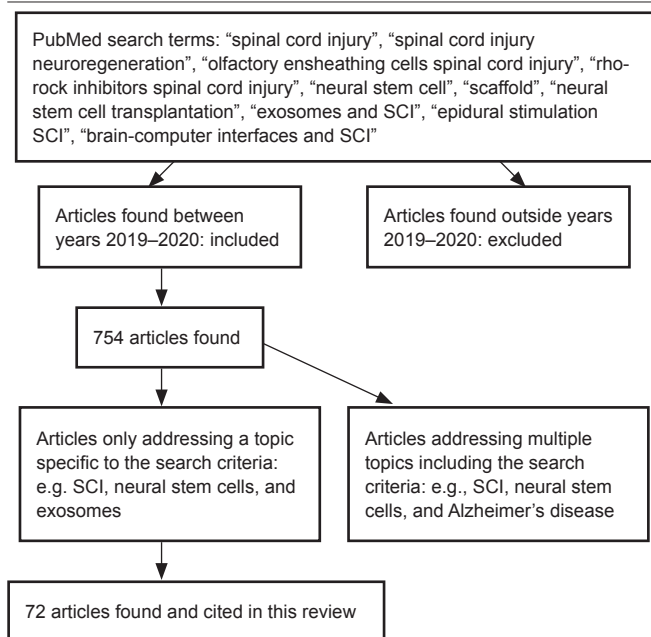
72 articles found and cited in this review

Figure 1 │ **Selection criteria for the literature included in this review.**
SCI: Spinal cord injury.

effects of the secondary SCI process. Furthermore, reactive oxygen species released by the inflammatory cells also contribute to SCI. SCI can disrupt Ca^{2+} homeostasis leading to hypocalcemia which can cause mitochondrial dysfunction eventually leading to apoptosis (Ahuja et al., 2017). Because inflammation is relatively well understood, this aspect of secondary SCI is a common target of neuroprotective agents.

Both primary and secondary SCI enhance the extracellular and intracellular mechanisms responsible for preventing CNS axon regeneration. A perineural net is a common extracellular matrix structure that is thought to play a role in limiting axon regeneration based on its intrinsic functions (Reichelt et al., 2019). Perineural nets help stabilize synaptic connectivity to regulate neuronal plasticity, form a physical and electrochemical barrier to prevent entry of noxious neurochemical stimuli, and sequester various molecules that would impede synapse formation (Reichelt et al., 2019). Altering the actions of the perineural nets is believed to potentially benefit neural regeneration.

An important intracellular regeneration mechanism impeded by primary and secondary SCI is growth cone formation. Growth cone formation is dependent on microtubule stabilization when promoting axon growth (Tedeschi et al., 2019). The process of actin treadmilling, the assembly of actin filaments at the tip of the growth cone and the disassembly of actin filaments in the central domain of the growth cone, is essential for growth cone motility, axon regeneration, and neurite formation (Tedeschi et al., 2019). Tedeschi et al. refer to the growth cone as the "sensory and motor organ" at the tip of growing axons.

Neuroprotective Agents: Pharmacologic

Methylprednisolone

Methylprednisolone is a synthetic glucocorticoid commonly used in the management of SCI. It has been shown to increase anti-inflammatory cytokine release and decrease membrane lipid peroxidation (Ahuja et al., 2017; Shah et al., 2020). Ahuja et al. (2017) and Shah et al. (2020) both noted a 2012 Cochrane meta-analysis showing at a 48-hour high dose protocol, methylprednisolone had complications with pneumonia, wound infections, as well as gastrointestinal hemorrhage. However, a lower dose 24-hour protocol showed

a 4-point improvement on the National Acute SCI study motor score when given within 8 hours of the SCI. Therefore, methylprednisolone can be used in certain SCI cases assuming the complications are understood and no contraindications present (Ahuja et al., 2017).

Riluzole

Riluzole is a benzothiazole sodium channel blocker that prevents excitotoxic cell death by inhibiting glutamate release (Ahuja et al., 2017; Tetreault et al., 2020). When sodium enters the neuron, it activates calcium channels on the neuron cell membrane leading to pre-synaptic glutamate release and therefore excitotoxic action potentials (Tetreault et al., 2020). A review published by Tetreault et al. (2020) focused on riluzole administration and neurobehavioral outcomes in rats. The most common tool to measure locomotor improvement was the Basso, Beattie, Besnahan score while the von Frey Filament test was used to measure responses to noxious stimuli (Tetreault et al., 2020). The review concluded Riluzole greatly improved locomotor scores, gait parameters, and responses to noxious stimuli. Riluzole has yet to be tested in a clinical setting, however, these promising results make the leap to clinical trials more plausible.

Neuroprotective Agents: Non-Pharmacologic

Cerebrospinal fluid drainage and mean arterial pressure augmentation

CSF drainage prevents spinal cord hypoperfusion by removing any impedance of blood flow to the site of injury after acute spinal cord infarction (Martirosyan et al., 2015; Ahuja et al., 2017). Mean arterial pressure (MAP) augmentation has been shown to improve SCI outcomes when MAP is maintained between 85 and 90 mmHg for 7 days after SCI according to AANS/CNS guidelines (Ahuja et al., 2017). The combination of cerebrospinal fluid (CSF) drainage and MAP augmentation increases the blood supply and perfusion pressure of the spinal cord to reduce ischemic damage.

Therapeutic hypothermia

Therapeutic Hypothermia for treatment of SCI involves cooling either the entire subject or the specific section of the injured spinal cord to 32–34°C immediately after injury (Kafka et al., 2020). Studies often use a treatment duration of 24–48 hours, decreasing temperature by 0.1°C per hour. There has been a plethora of studies done on the effects of hypothermia on SCI. However, the exact mechanism by which hypothermia reduces the process of secondary SCI is poorly understood. Hypothermia has been shown to reduce the basal metabolic rate in the CNS as well as decrease inflammation around the site of injury (Khorasanizadeh et al., 2017). Moreover, hypothermia reduces blood flow, free radical production, and lactate formation around the site of injury (Kafka et al., 2020). Ahn et al. (2020) studied the effectiveness of hypothermia in improving hind limb motor outcomes in rats based on a reduction of oxidative stress and inflammation around the site of injury. One aspect of their study compared activation rates of Iba-1 immunoreactive microglia in the ventral horn of rats in normothermic and hypothermic conditions after lumbar SCI. They saw a 40%, 130%, and 220% decrease in activation over 12-hour, 1-day, and 2-day periods, respectively in the ventral horn of the hypothermic rats (Ahn et al., 2020). They concluded hypothermia has very promising therapeutic advantages as their results showed not only a marked decrease in supraoxide anion (8OHdG) levels, but also an increase in endogenous antioxidant levels (SOD1, SOD2, CAT, and GPX). Hypothermia could also decrease free radical generation, inhibit excitotoxicity and apoptosis, and promote angiogenesis to mitigate axonal damage and enhance neurogenesis (Wang and Pearse, 2015).

A vast majority of studies focusing on hypothermia only

report pre-clinical data. The results of some clinical trials have been promising. Kafka et al. (2020) mentioned a few studies completed between 2009 and 2014 that focused on the effects of local and systemic hypothermia in human clinical trials. Local hypothermia involves cooling the local area of injury through transcutaneous, intrathecal, paraspinal, epidural injections or through a heat exchanger cooling system directly over the injury. Systemic hypothermia involves cooling the entire body through methods like air and water cooling blankets, ice packs, hydrogel-water circulating pads, and cooling vests (Kafka et al., 2020). Hypothermic conditions were often coupled with glucocorticoids or methylprednisolone and surgical decompression. The patients showed more promising recoveries than expected when compared to patients with no treatment.

More clinical trials need to be completed before local or systemic hypothermic treatments can be considered an effective clinical treatment modality. A double-blind study involving many people analyzing therapeutic effectiveness of hypothermia across a wide temperature range and variations in treatment duration would be a good start (Kafka et al., 2020).

Neuroregenerative Agents: Pharmacologic
Rho-rock inhibitors
The Rho protein family consists of 22 GTPases responsible for the regulation of actin dynamics to control cell shape and motility. Signal transduction for Rho proteins is aided by activation of ROCK, a serine-threonine kinase that activates downstream enzymes Lim kinase and cofilin causing growth cone collapse (Forgione and Fehlings, 2014). The Rho-Rock pathway provides a barrier to axon regeneration based on its downstream activity. Forgione and Fehlings (2014) depict how the Rho-ROCK pathway becomes activated through surface oligodendrocyte glycoproteins (SOPs). Some SOPs include myelin-associated glycoprotein, oligodendrocyte-myelin glycoprotein, and the Nogo-A molecule. SOPs bind to receptors, NgR, p75, and LINGO1 on the surface of the neuron to activate Rho proteins (Forgione and Fehlings, 2014).

Ahuja et al. (2017) discussed the outcome of a study done on Cethrin/VX-210, a potential pharmacologic inhibitor of the Rho-ROCK pathway. In a mixed open-label phase trial, Cethrin was given to 48 patients with both thoracic and cervical SCIs and was found to have no serious adverse effects while significantly improving ASIA motor scores. Cethrin is also known as rho-antagonist BA-210 (Forgione and Fehlings, 2014). The multi-center, double-blind, placebo-controlled clinical trial (phase 2b/3) to evaluate cethrin's safety and efficacy for acute traumatic cervical SCI is ongoing (NCT02669849) (Fehlings et al., 2018).

Anti-NOGO approaches
Due to the shear complexity of the Rho-Rock pathway, a number of rat and primate studies have been published focusing on targeting specific aspects of it. Another common approach to inhibiting this pathway has been through the Nogo-A molecule/NgR receptor complex. Anti-Nogo is a monoclonal antibody meant to bind SOP Nogo-A and prevent it from binding to the NgR receptor complex on the neuronal surface (Ahuja et al., 2017; Mohammed et al., 2020; Shah et al., 2020). Monoclonal antibodies are commonly used to target a wide variety of signaling pathways with remarkable specificity. Anti-nogo antibodies may be cheaper to develop and less labor-intensive in comparison to developing Rho-Rock inhibitors. Further data collection must be done before this method can be considered a viable means of treatment.

While these are not pharmacologic modalities, electroacupuncture and deep brain stimulation have been shown to be beneficial in NogoA/Rho-ROCK inhibition in rats as well (Xiao et al., 2019; Mohammed et al., 2020; Zheng et al., 2020). Clinical trials focusing on electroacupuncture and deep brain stimulation on NogoA/Rho-ROCK pathway inhibition have yet to take place.

Neuroregenerative Agents: Non-Pharmacologic
Stem cell therapy
Research focused on stem cell transplantation in SCI started roughly 50 years ago with clinical trials initiated recently (Assinck et al., 2017). Various cell types have been studied for their capacity to repair SCI with transplantation. The most widely studied cell types in SCI transplantation are neural stem and progenitor cells (NSPCs), oligodendrocyte progenitor cells (OPCs), mesenchymal stem cells (MSCs), Schwann cells, and olfactory ensheathing cells (OECs) (Assinck et al., 2017). OPCs are precursors of oligodendrocytes that are myelin-forming cells in the CNS (Miller, 1996). Schwann cells are myelinating cells of peripheral nerves. Extensive animal based studies have shown all these cell types are viable candidates for cell therapy mediating functional improvement in SCI through several mechanisms such as neuroprotection, axon sprouting and/or regeneration, immunomodulation, and myelin regeneration (Assinck et al., 2017). **Table 1** listed the completed and ongoing clinical trials of neural stem cell therapy in spinal cord injury patients and their current status.

NSPCs
NSPCs are multipotent progenitors with self-renewal capacity in the presence of growth factors and can differentiate into neurons, astrocytes, and oligodendrocytes in the absence of growth factors (Wetts and Fraser, 1988; Davis and Temple, 1994; Gage, 2000). Transplantation of NSPCs into the animal models of SCI has been shown to effectively promote neural regeneration leading to the recovery of motor function (Yousefifard et al., 2016; Qian et al., 2020; Zhu et al., 2020). Latest reviews of human clinical trials for stem cell therapies indicated that stem cell transplantations or cell based therapies in SCI appear to be safe without any serious adverse effects (Silvestro et al., 2020; Willison et al., 2020). However, findings of the completed human trials showed only limited improvement of sensory and motor function in patients with SCI (Silvestro et al., 2020). The reviews include both completed and ongoing human trials of stem cell therapy in SCI. Ongoing clinical trials are evaluating the efficacy of various types of stem cells including MSCs and NSCs. The most prominent challenges of the stem cell therapy are the inhospitable environment at the lesion site of the spinal cord that inhibits grafted cell survival, differentiation of the grafted cells into desired phenotypes, and formation of correct connections between host and grafted cells.

OECs
The primary olfactory nervous system is undergoing constant regeneration.

OECs are the glial cells found in the primary olfactory nervous system (Reshamwala et al., 2019). OECs are believed to play a vital role in regeneration of the olfactory nervous system because they provide structural, neurotrophic, and axonal guidance support to the olfactory axons from the lamina propria to the olfactory bulb (Reshamwala et al., 2019; **Figure 2**).

Moreover, OECs phagocytose foreign microbes and the cellular debris of olfactory nerve regeneration (Reshamwala et al., 2019). OECs are a current hot topic of SCI research because of their ability to help olfactory neurons regenerate. A promising *in vitro* study by Yue et al. (2020) focused on the Wnt/β-catenin neurotropic pathway in OECs and its ability to induce proliferation and differentiation of neural stem cells (NSCs). They found Wnt activated OECs were able to increase the percentage of Ki67/Sox2 double positive NSCs

compared to the control. Moreover, Wnt OECs prolonged nestin expression and increased differentiation of NSCs to Tuj1-positive neurons, indicating active neuronal proliferation. Therefore, combination of Wnt OECs and NSCs may be beneficial to the efficacy of SCI transplantations.

One topic of current OEC SCI research focuses on the

Figure 2 | Schematic illustration of the location of OECs in the primary olfactory nervous system.
Human olfactory nerves and bulbs are highlighted in yellow. The amplified diagram illustrates that OECs (dark red) ensheath the axons of the olfactory neurons (ON, green) that transverse the cribriform plate (CP) from the lamina propria to the olfactory bulb (OB). Additional abbreviations: GM: Glomeruli; OE: olfactory epithelium; OM: olfactory mucosa (pink area); SC: sustentacular cells. Adapted from Reshamwala et al. (2019).

survivability and integration of OECs after transplantation into the spine. Reshamwala et al. (2019) reviewed the past ten years' OEC studies to analyze what factors were most important in maximizing the efficacy of transplanted OECs. The factors they considered included: injury type, source of transplanted cells, co-transplantation with other cell types, number and concentration of cells, method of delivery, and time of transplantation after the injury. Two factors were found to be of upmost importance when promoting survival of transplanted OECs: the ability to identify the transplanted OECs in the recipient as well as type of delivery system for the OECs. They found a majority of OEC transplantation studies never commented on their OEC survivability after transplantation. Therefore, having a way to track and quantify OECs after transplantation experiments is one more way to eliminate error when measuring the efficacy and survivability of the transplanted OECs. Of the 66 studies, 51 of them found OECs were able to remain at the site of SCI longer when used with a cell suspension or 3D delivery system including: mucosal pieces, matrices, gelatin sponges, and hydrogels (Reshamwala et al., 2019). From another study by Reshamwala et al. (2020) focused on OEC purity and how it affects transplant outcomes. OECs can be harvested from the lamina propria inferior to the neuroepithelium or directly from the olfactory bulb in the anterior cranial fossa (Reshamwala et al., 2020). OECs harvested from the olfactory mucosa often contain fibroblasts, glial cells, and other supporting cells while those harvested from the olfactory bulb are not accompanied by any supporting cells (Reshamwala et al., 2020). It was unclear in OEC research whether or not fibroblasts, glial cells, and other supporting cells, when taken with OECs from the donor, positively or negatively impacted the transplant

Table 1 | Completed and ongoing clinical trials of neural stem cell therapy in spinal cord injury

Study title/ clinical trial identifier	Phase	No. of patients recruited	Type of cells transplanted	Route of administration	Dosage/duration of treatment	Status	Drop-out rate	Outcome	Adverse effects
Study of human central nervous system stem cells (HuCNS-SC) in patients with thoracic spinal cord injury (NCT01321333)	I/II	12 patients (18–60 yr)	HuCNS-SC	Intramedullary transplantation of HuCNS-SC	Single dose of cells (number of cells not available) followed by immunosuppression for 9 mon	Completed (3/2011–6/2015)	0	N/A	N/A
Long-term follow-up of transplanted human central nervous system stem cells (HuCNS-SC) in spinal cord trauma subjects (NCT01725880)	I/II	12 patients (18–65 yr)	HuCNS-SC	Intramedullary transplantation of HuCNS-SC	Single dose of cells (number of cells not available)	Terminated (11/2012–6/2016)	0	N/A	N/A
Study of human central nervous system (CNS) stem cell transplantation in cervical spinal cord injury (NCT02163876)	II	31 patients (18–60 yr)	HuCNS-SC	Intramedullary transplantation of HuCNS-SC	Single dose of cells (number of cells not available)	Terminated (10/2014–5/2016)	0	N/A	N/A
Dose escalation study of AST-OPC1 in spinal cord injury (NCT02302157)	I/II	25 patients (18–69 yr)	AST-OPC1	N/A	One injection of 2 million or 10 million AST-OPC1, or 2 injections of 10 million AST-OPC1 for a total of 20 million cells	Completed (3/2015–12/2018)	0	N/A	N/A
Safety study of human spinal cord-derived neural stem cell transplantation for the treatment of chronic SCI (NCT01772810)	I	8 patients (planed) (18–65 yr)	Human spinal cord stem cell	Surgical implantation	Human spinal cord stem cell implantation (number of cells not available)	Ongoing (8/2014–12/2022)	N/A	N/A	N/A
Safety stem cells in spinal cord injury (NCT04205019)	I	10 patients (planed) (18–40 yr)	Neuro-Cells	Intrathecal administration of Neuro-Cells	Single dose of Neuro-Cells (number of cells not available)	Ongoing (11/2020–3/2022)	N/A	N/A	N/A
Clinical study of an autologous stem cell product in patients with a (sub)acute spinal cord injury (NCT03935724)	II/III	70 patients (planed) (18–65 yr)	Neuro-Cells	N/A	Single dose of Neuro-Cells (number of cells not available)	Ongoing (6/2021–12/2022)	N/A	N/A	N/A

AST-OPC1: Oligodendrocyte progenitor cells; HuCNS-SC: human central nervous system stem cells; N/A: not available. Data were collected from https://clinicaltrials.gov/.

outcomes. Reshamwala et al. (2020) concluded that olfactory bulb-derived OECs had better outcomes of transplantation when harvested directly from the olfactory bulb without the accompanying cells and fibroblasts. When OEC transplantation is successful, OECs have been shown to improve recovery of proprioception in animal models with reapposed dorsal roots after brachial plexus avulsion injuries (Ahuja et al., 2017). Direct transplantation of OECs to the spinal cord can improve OEC efficacy and decrease time of action, however, transplantation can sometimes cause further damage to the surrounding tissues counteracting the neurotropic effects of OECs.

Zhang et al. (2019) studied the effectiveness and feasibility of IV transplantation of OECs in rats. OECs were labeled with quantum dots (combined with calcein acetoxymethyl ester) and their biodistribution was tracked using an Olympus confocal fluorescence imaging system. They noticed accumulation of labeled OECs at the site of SCI happened in as soon as 10 minutes and peaked at 7 days. Motor function, neural growth, remyelination, all improved with IV transplantation in comparison to the group only injected with quantum dots. Inflammation was reduced as well.

As researchers better understand OECs mechanism of action for neuronal support and repair, the study by Chen et al. (2020) may be insightful. Chen et al. (2020) studied how 2-methoxy-1,4-naphthoquinone, a natural compound isolated from *Impatiens balsamina* and *Impatiens glandulifera*, affects the proliferation, migration, and phagocytic activity of OECs in mice. Using fluorescent cell markers, flow cytometry, and fluorescence microscopy, the study found this compound increased proliferative, mitotic, and phagocytic activity of the OECs. Chen et al. (2020) also identified the OEC gene Nrf2 as the target of this compound.

Olfactory ensheathing cells have a promising outlook for future SCI research because of their unique properties and actions. Another unique property of OECs is their lack of neoplastic transformation. Only 11 OEC tumors, all benign, have been known to exist and they often resemble Schwannomas (Murtaza et al., 2019). OEC's low neoplastic transformation rate was analyzed by Murtaza et al. (2019), and the group determined it stemmed from their inherent supportive, neurotropic, and phagocytic roles of OECs.

Further research on OECs must be done to understand exactly how the supportive, neurotropic, and phagocytic mechanisms work, however, there is a good amount of research showing promising results for OECs as a viable treatment for SCI.

Biomaterial scaffold and stem cell transplantation in spinal cord injury

In SCI, transplantation of stem cells alone is not enough to promote regeneration of injured nerves due to the hostile environment at the injured site of the spinal cord (Silvestro et al., 2020). The extracellular environment plays a significant role in controlling cellular behavior including cellular growth and differentiation (Streuli, 1999; Sharma et al., 2020a, 2020b). Transplanted cells can survive and differentiate into desired cell types in the presence of a suitable extracellular environment. Many different types of scaffolds, made up of natural matrix, like matrigel and its components such as collagen, laminin, fibronectin or artificial biomaterials have been studied in transplantation experiments (Hwang et al., 2008; Madaghiele et al., 2008; Katoh et al., 2019; Wang et al., 2020). Transplantation of collagen scaffold modified with N-cadherin (Liu et al., 2020b), mixture of primary NSCs and matrigel (Wang et al., 2020), collagen/silk fibroin 3D-scaffold along with NSCs (Jiang et al., 2020) into complete transected rat spinal cord showed comparable outcomes following SCI in rodents.

Artificial biomaterial substrates such as chitosan, agarose, polymethacrylamide, polylactic co-glycolic acid etc. have been studied as scaffolds to treat SCI (Li et al., 2019; Ham et al., 2020; Jiang et al., 2020; Kim et al., 2020; Ma et al., 2020; Zhang et al., 2020a; Zhong et al., 2020b). These studies showed significant locomotor recovery and formation of microvascular structure (Zhong et al., 2020b), reduced inflammation and glial scar formation, increased density of axons growing into the injury site, and improved neurovascular interaction between microvessels and host axons (Tran et al., 2020). Ji et al. (2020) reported scaffold transplantation induced alleviation in pathological changes such as smoother spinal cord, less scar tissue and lower inflammatory activity in SCI after transplantation of silk fibroin/chitosan scaffold in combination with adipose-derived stem/stromal cells over expressing brain-derived neurotrophic factor and neurotrophin-3.

Inflammation is an important player that inhibits endogenous NPC migration and their differentiation into neurons at the injured site in SCI. A recent study by Ma et al. (2020) has shown that inhibition of microglia/macrophage-mediated inflammation promotes neurogenesis of endogenous NPCs and improves functional recovery. Transplantation of methacrylated gelatin hydrogel scaffold coupled with colony stimulating factor 1 receptor inhibitor in the mouse spinal cord with complete transection produced significant reduction of CD68-positive microglia/macrophages and mRNA levels of pro-inflammatory factors, and increase in the number of neurons in the lesioned area (Ma et al., 2020).

In a recent study, Deng et al. (2020) have reported encouraging results of animal experiments and a phase I clinical trial. Transplantation of collagen scaffold and human umbilical cord mesenchymal stem cells in acute spinal cord injury in rats and dogs demonstrated significant motor function recovery shown by the Basso, Beattie, Besnahan locomotor scale in rats and the Olby scoring scale in dogs. Neurological function was also enhanced in both species after 8 weeks and 6 months of the transplantation, respectively. In a phase I clinical trial conducted by the same group, transplantation of human umbilical cord mesenchymal stem cells and collagen scaffold in patients with acute complete cervical cord injuries showed increased sensory and motor functions measured by the American Spinal Injury Association scores and the activities of daily life scores during 12 months follow up (Deng et al., 2020). The patients also restored bowel and urinary function, and formed new neural connections shown by magnetic resonance imaging.

While the aforementioned studies have shown promising results, they have failed to report long distance regeneration of motor nerves that cross the lesion gap in complete SCI model after the transplantation of scaffolds along with stem cells. A recent study by the Mark Tuszynski group showed a remarkable regeneration of host axons into the transplanted 3D biomimetic scaffold and readily passed across host/scaffold interfaces (Koffler et al., 2019). This study along with others (Spilker et al., 2001) suggest that longitudinal channels are important structures in 3D biomimetic scaffolds for extensive regeneration of host axons to cross the lesion site, and linear growth of grafted cell-derived axons out of the scaffold.

Biocompatibility and slow biodegradation are essential requirements for *in vivo* application of artificial scaffolds. Zhang et al. (2020a) have reported about 60% degradation of a composite hydrogel within 21 days of subcutaneous transplantation in rats. Koffler et al. (2019) have also reported 49% reduction in the thickness of the scaffold wall compared with pre-implantation size 6 months after the scaffold transplantation in SCI rats. These results suggest that hydrogel-based biomaterials could be advantageous for SCI therapy.

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Exosomes for spinal cord injury repair

Exosomes are membrane bound vesicles 30–150 nm in diameter released by various cells and can carry intracellular contents including proteins, lipids, mRNA, and microRNA (Tkach and Théry, 2016). Several studies have reported the importance of micro RNAs (miRNA) in SCI. miRNAs are small noncoding RNAs that regulate RNA silencing and post-transcriptional modification of gene expression. More importantly, miRNA-126 has been shown to promote angiogenesis and reduce inflammation after SCI. Recently, Huang et al. (2020) used MSC derived exosomes to deliver miRNA-126 to cure SCI in rats. Administration of exosomes derived from miRNA-126 transfected MSCs promoted angiogenesis and neurogenesis at the injury site of SCI. Further, their results showed that miRNA-126 treated animals with SCI had increased Bax and caspase-3 expression and increased Bcl2 expression, suggesting that miRNA-126 loaded exosomes inhibited apoptosis.

Zhong et al. (2020a) have reported the effect of exosomes derived from neural stem cells on angiogenesis in SCI in rats. NSC-derived exosomes promoted angiogenesis at injured area of the spinal cord by upregulating vascular endothelial growth factor-A.

On site delivery of exosomes was shown to be an efficient strategy of exosome delivery in SCI. In a study by Li et al. (2020c), transplantation of MSC-derived exosomes immobilized in a peptide-modified adhesive hydrogel in rat SCI resulted in neural and bladder function recovery after 28 days of transplantation.

Other exosome delivery methods also show promising results. Intravenously injected exosomes derived from MSCs transfected with miRNA-544 into SCI in rats showed neuronal functional recovery and reduced inflammation following SCI (Li et al., 2020a). A study using SCI model reported that exosomes derived from MSCs under hypoxia promotes functional recovery following SCI in mice (Liu et al., 2020a). They claimed the functional recovery following SCI was possibly due to microglial polarization shifting from M1 to M2 phenotype by hypoxic exosomes (Liu et al., 2020a). A similar study by Shao et al. (2020) has shown that exosomes obtained from adipose tissue-derived MSCs under hypoxic condition were more effective in functional recovery following SCI in rats compared to the exosomes derived from the MSCs under normoxic conditions. Luo et al. (2020) reported the potential effect of G-protein-coupled receptor kinase 2 internalizing protein 1 (GIT1) overexpressing exosomes derived from MSCs on functional recovery following SCI in rats. G-protein-coupled receptor kinase 2 internalizing protein 1 is involved in cell spreading, adhesion and migration, synaptic formation, and cytoskeletal organization.

Exosomes derived from bone marrow-derived MSCs were found to enhance LC3IIIB and Beclin-1 autophagy-related proteins (Gu et al., 2020). Further, there was a decline in the expression of caspase-3 and upregulation of Bcl-2 (Gu et al., 2020). These results suggest that BM-MSCs derived exosomes can prevent neuronal apoptosis following SCI.

Epidural stimulation to treat spinal cord injury

Both preclinical and clinical studies on epidural electrical stimulation (EES) of spinal cord have shown encouraging sensory and motor function improvement following SCI. After the first clinical study by Harkema et al. (2011), small number of clinical trials have been conducted on testing EES in SCI. Although precise mechanism of action of EES has not been reported, a recent study by Ghorbani et al. (2020) have shown the activation of Wnt signaling cascade after EES in rat models of SCI. Another preclinical study by Li et al. (2020b) have shown that EES of spinal cord promotes oligodendrocyte survival and enhance differentiation of oligodendrocytes by downregulating bone morphogenetic protein 4 and p-Smad1/5/9. Several studies have demonstrated the regulation of oligodendrocyte development by Wnt signaling (Shimizu et al., 2005; Dai et al., 2014).

There are some complications for EES reviewed by Taccola et al. (2020). Transplanted epidural electrode may not be effective over long period of time due to formation of encapsulating mass formed by glial cells and fibrous connective tissue around the transplanted electrode. Further, the electrode may get displaced from its transplanted site causing infection and even injury to the spinal cord. Important barriers for implementation of EES in SCI patients include need for more studies confirming the efficacy of EES, lack of clear stimulation guidelines, and selection of patients with SCI for EES (Taccola et al., 2020).

Brain-computer interfaces

Research regarding brain-computer interfaces (BCIs) for the management of spinal cord injury has shown promising results in restoring both gross and fine locomotion in paralyzed patients. BCIs seek to decode motor or cognitive intentions from the brain and translate the intentions to an effector: a mouse cursor on a screen or a robotic arm for example (Jarosiewicz et al., 2015). A BCI apparatus involves the following: electrodes placed directly on the brain tissue or in the epidural, subdural, or subarachnoid spaces, a device containing neural mapping algorithms known as a decoder, and an effector that the SCI patient would like to control (Jarosiewicz et al., 2015). The decoder uses a pre-made algorithms to translate specific patterns of cortex excitement into a meaningful signal for the effector. In certain scenarios, presumably when use of electrodes is contraindicated, real-time magnetic resonance imaging is used in place of electrodes to map blood-oxygen levels in the brain to transmit a signal to the decoder (Zheng et al., 2020). Yang et al. (2020) reviewed multiple clinical studies where BCIs helped to momentarily restore locomotion to limbs. There was a clinical study where two quadriplegic patients were able to control and perform 3D movements like grasping and stretching using a robotic arm connected to a BCI successfully (Yang et al., 2020). A study showed that patients successfully controlled an exoskeleton through an epidural wireless BCI (Benabid et al., 2019).

Results from various clinical studies of BCI and locomotor improvement are nothing short of astounding. However, each study seems to encounter the same problem—nonstationarity. Because of the inherent plasticity of the brain, signals received by the decoder for a particular movement change over time (Jarosiewicz et al., 2015). This leads to decreased accuracy of the movement by the BCI and therefore constant recalibration of the decoder is required to account for nonstationarity. Recalibration of the decoder often has to be done every few minutes, making BCIs impractical for real world use. Calibration of the decoder involves statistically modeling neural activity and movement intention by having the patient imagine moving the effector from one predetermined location to another (in the case of a mouse pointer from one location on the screen to another) (Jarosiewicz et al., 2015). Jarosiewicz et al. (2015) studied the effects of calibrating the decoder in a different way from previous BCI studies. They used a technique called retrospective target interference. In retrospective target interference, the patient decides where and when they would like to move the effector as opposed to following predetermined locations in the standard calibration technique. Therefore, researchers retrospectively infer the patient's intended movement. The research group found they were able to recalibrate the decorder anywhere from 2.2 to 94.5 minutes compared to the standard recalibrating procedure of 5.5 to 45.8 minutes (Jarosiewicz et al., 2015).

Very promising results of BCI as a modality to manage SCI have been shown by multiple studies. With further research into the effects of nonstationarity on the accurancy of BCI coordinated movements, this modality may become a viable means of restoring a meaningful quality of life to those who suffer from SCI.

Future Directions

With each treatment modality in the adolescent stages of research, further data collection must be done in order to understand how each treatment affects the SCI recovery process. Understanding the mechanism of action behind each modality may be beneficial not only to the field of SCI research, but also to research regarding peripheral nervous system injuries. A study by Zhang et al. (2020b) looked at the potential benefit of combining OECs and mesenchymal stem cell exosomes for sciatic nerve injury recovery in rats. Nerve injuries often result in hypoxic environments which are deleterious to OEC survival. They found combining human umbilical cord-derived mesenchymal stem cell exosomes with OECs improved survival of OECs in the hypoxic environment by 1.76 to 4.62 fold. Sciatic nerve conduction improved and the rats showed increased motor and sensory function based on an increased score on the Sciatic Function Index (Zhang et al., 2020b).

Furthermore, understanding the signaling activation of different stem cells may prove beneficial if researchers would like to develop treatments that mimic different aspects of the OEC-mediated olfactory regeneration process. For example, macrophage migration inhibitory factor and its binding partner HTRA1 were found to not only minimize macrophage population of the olfactory nerves, but also promote OEC phagocytosis of neural debris. Migration inhibitory factor inhibits HTRA1 to influence migration and proliferation of OECs (Wright et al., 2020) .

Another potential area of study would be combining different modalities to see if there is an increase in efficacy over a singular modality. Using methylprednisolone with Rho-Rock inhibitors may prove to be more effective than simply using Rho-Rock inhibitors alone for SCI treatment. Exosomes and artificial scaffolds may be a great delivery system not only for biomolecules, but also for pharmacologic options. In addition, electrical stimulation of the spinal cord may be combined with the variety of stem cell therapies to promote the crosstalk between the grafted cells and the host cells to greatly facilitate functional recovery. **Table 2** listed the clinical trials of the current pharmacological and non-pharmacological therapies for the spinal cord injury patients.

Table 2 | Clinical trials of pharmacological and non-pharmacological therapy in spinal cord injury

Therapeutic agent	Clinical Trial ID	Clinical trial name	Type of clinical trial	Number of patients in trial	Period of treatment	Dosage	Number of patients positively affected by treatment	Adverse effects	No. of dropouts
Methylprednisolone	NCT00004759	Methylprednisolone given by 24-Hour or 48-Hour Infusion Versus Tirilazad for Acute Spinal Cord Injury	Multi-center, double-blind	497 (14 yr and older)	24 h (166 patients) or 48 h (167 patients) The treatment was started within 8 h of the insult. The remaining 166 patients received tirilazad mesylate	All patients received IV boulus dose of 30 mg/kg before treatment 24 h period patients received IV infusion at 5.4 mg/kg/h 48 h period patients received IV infusion at 5.4 mg/kg/h	ASIS scores were measured at 6 wk, 6 mon, and 1 yr post treatment. For both the 24 and 48 h duration, patients showed increased ASIS scores at each time interval	Pneumonia, sepsis, gastrointestinal hemorrhage, death 9 patients showed pneumonia at 6 wk 4 patients showed sepsis at 6 wk Exact number for GI hemorrhage were not reported 10 patients had died within 1 yr of treatment	12 patients for both 24- and 48-h treatment durations
Therapeutic Hypothermia	PMID: 24628130	Local cooling for traumatic spinal cord injury: outcomes in 20 patients and review of the literature	N/A	20	4 h (started within 8 h of SCI)	Dural temp cooled to 6°C using suspended extradural saddle	12 patients showed ASIA improvement	N/A	0
Rho-Rock Inhibitors	NCT02669849	Study to assess the efficacy and safety of VX-210 in subjects with acute traumatic cervical spinal cord Injury	Multi-center, double- blind, placebo controlled	70	N/A VX-210 was given within 72 h of insult	3 or 9 mg of VX-210	N/A	N/A	44 (as of January 4, 2021)
Epidural Stimulation-Harkema's Study	NCT02339233	Epi Stim to Facilitate Standing and Stepping	N/A	1	Stimulation lasted 40 to 120 min	Stimulation amplitude-0.5 to 10.0 V stimulation frequency- 5 to 40 Hz	1-patient was able to dorsiflex their ankle and even gained some control of bowel and bladder function	Minor irritation at electrode implant site, minor paresthesias	0
Brain-Computer Interfaces	1. NCT00912041 2. NCT02550522	1. BrainGate2: Feasibility Study of an Intracortical Neural Interface System for Persons With Tetraplegia 2. Brain Computer Interface: Neuroprosthetic Control of a Motorized Exoskeleton (BCI)	N/A	N/A	N/A	N/A	N/A	N/A	N/A

ASIA: American Spinal Injury Association; IV: intravenous; N/A: not available; SCI: spinal cord injury. Data were collected from https://clinicaltrials.gov/.

Review

Conclusions

There is a plethora of promising research currently being done to combat the devastating impact of SCI. However, a majority of the research is still in its adolescent stage and positive clinical outcomes have yet to be demonstrated. Moreover, there is a lack of research to explore the effects of combining different modalities that may produce larger, synergistic benefits to the patients. More data need to be collected before the aforementioned modalities can be considered viable treatment options.

References

Ahn JH, Lee TK, Kim B, Lee JC, Tae HJ, Cho JH, Park Y, Shin MC, Ohk TG, Park CW, Cho JH, Hong S, Park JH, Choi SY, Won MH (2020) Therapeutic hypothermia improves hind limb motor outcome and attenuates oxidative stress and neuronal damage in the lumbar spinal cord following cardiac arrest. Antioxidants 9:38.

Ahuja CS, Nori S, Tetreault L, Wilson J, Kwon B, Harrop J, Choi D, Fehlings MG (2017) Traumatic spinal cord injury- Repair and regeneration. Clin Neurosurg 80:S22-90.

Assinck P, Duncan GJ, Hilton BJ, Plemel JR, Tetzlaff W (2017) Cell transplantation therapy for spinal cord injury. Nat Neurosci 20:637-647.

Benabid AL, Costecalde T, Eliseyev A, Charvet G, Verney A, Karakas S, Foerster M, Lambert A, Morinière B, Abroug N, Schaeffer MC, Moly A, Sauter-Starace F, Ratel D, Moro C, Torres-Martinez N, Langar L, Oddoux M, Polosan M, Pezzani S, et al. (2019) An exoskeleton controlled by an epidural wireless brain–machine interface in a tetraplegic patient: a proof-of-concept demonstration. Lancet Neurol 18:1112-1122.

Chen M, Vial ML, Gee L, Davis RA, St John JA, Ekberg JAK (2020) The plant natural product 2-methoxy-1,4-naphthoquinone stimulates therapeutic neural repair properties of olfactory ensheathing cells. Sci Rep 10:1-15.

Courtine G, Sofroniew MV (2019) Spinal cord repair: advances in biology and technology. Nat Med 25:898-908.

Dai ZM, Sun S, Wang C, Huang H, Hu X, Zhang Z, Lu QR, Qiu M (2014) Stage-specific regulation of oligodendrocyte development by Wnt/β-catenin signaling. J Neurosci 34:8467-8473.

Davis AA, Temple S (1994) A self-renewing multipotential stem cell in embryonic rat cerebral cortex. Nature 372:263-266.

Deng WS, Ma K, Liang B, Liu XY, Xu HY, Zhang J, Shi HY, Sun HT, Chen XY, Zhang S (2020) Collagen scaffold combined with human umbilical cord-mesenchymal stem cells transplantation for acute complete spinal cord injury. Neural Regen Res 15:1686-1700.

Fehlings MG, Kim KD, Aarabi B, Rizzo M, Bond LM, McKerracher L, Vaccaro AR, Okonkwo DO (2018) Rho inhibitor VX-210 in acute traumatic subaxial cervical spinal cord injury: design of the spinal cord injury Rho INhibition InvestiGation (SPRING) clinical trial. J Neurotrauma 35:1049-1056.

Forgione N, Fehlings MG (2014) Rho-ROCK inhibition in the treatment of spinal cord injury. World Neurosurg 82:E535-539.

Gage FH (2000) Mammalian neural stem cells. Science 287:1433-1438.

Ghorbani M, Shahabi P, Karimi P, Soltani-Zangbar H, Morshedi M, Bani S, Jafarzadehgharehziaaddin M, Sadeghzadeh-Oskouei B, Ahmadalipour A (2020) Impacts of epidural electrical stimulation on Wnt signaling, FAAH, and BDNF following thoracic spinal cord injury in rat. J Cell Physiol 235:9795-9805.

Gu J, Jin ZS, Wang CM, Yan XF, Mao YQ, Chen S (2020) Bone marrow mesenchymal stem cell-derived exosomes improves spinal cord function after injury in rats by activating autophagy. Drug Des Devel Ther 14:1621-1631.

Ham TR, Pukale DD, Hamrangsekachaee M, Leipzig ND (2020) Subcutaneous priming of protein-functionalized chitosan scaffolds improves function following spinal cord injury. Mater Sci Eng C 110:110656.

Harkema S, Gerasimenko Y, Hodes J, Burdick J, Angeli C, Chen Y, Ferreira C, Willhite A, Rejc E, Grossman RG, Edgerton VR (2011) Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. Lancet 377:1938-1947.

Huang JH, Xu Y, Yin XM, Lin FY (2020) Exosomes derived from miR-126-modified MSCs promote angiogenesis and neurogenesis and attenuate apoptosis after spinal cord injury in rats. Neuroscience 424:133-145.

Hwang NS, Varghese S, Elisseeff J (2008) Controlled differentiation of stem cells. Adv Drug Deliv Rev 60:199-214.

Jarosiewicz B, Sarma AA, Bacher D, Masse NY, Simeral JD, Sorice B, Oakley EM, Blabe C, Pandarinath C, Gilja V, Cash SS, Eskandar EN, Friehs G, Henderson JM, Shenoy K V., Donoghue JP, Hochberg LR (2015) Virtual typing by people with tetraplegia using a self-calibrating intracortical brain-computer interface. Sci Transl Med 7:313ra179.

Ji WC, Li M, Jiang WT, Ma X, Li J (2020) Protective effect of brain-derived neurotrophic factor and neurotrophin-3 overexpression by adipose-derived stem cells combined with silk fibroin/chitosan scaffold in spinal cord injury. Neurol Res 42:361-371.

Jiang JP, Liu XY, Zhao F, Zhu X, Li XY, Niu XG, Yao ZT, Dai C, Xu HY, Ma K, Chen XY, Zhang S (2020) Three-dimensional bioprinting collagen/silk fibroin scaffold combined with neural stem cells promotes nerve regeneration after spinal cord injury. Neural Regen Res 15:959-968.

Kafka J, Lukacova N, Sulla I, Maloveska M, Vikartovska Z, Cizkova D (2020) Hypothermia in the course of acute traumatic spinal cord injury. Acta Neurobiol Exp (Wars) 80:172-178.

Katoh H, Yokota K, Fehlings MG (2019) Regeneration of spinal cord connectivity through stem cell transplantation and biomaterial scaffolds. Front Cell Neurosci 13:248.

Khorasanizadeh MH, Eskian M, Vaccaro AR, Rahimi-Movaghar V (2017) Granulocyte colony-stimulating factor (G-CSF) for the treatment of spinal cord injury. CNS Drugs 31:911-937.

Kim BJ, Choi JY, Choi H, Han S, Seo J, Kim J, Joo S, Kim HM, Oh C, Hong S, Kim P, Choi IS (2020) Astrocyte-encapsulated hydrogel microfibers enhance neuronal circuit generation. Adv Healthc Mater 9:e1901072.

Koffler J, Zhu W, Qu X, Platoshyn O, Dulin JN, Brock J, Graham L, Lu P, Sakamoto J, Marsala M, Chen S, Tuszynski MH (2019) Biomimetic 3D-printed scaffolds for spinal cord injury repair. Nat Med 25:263-269.

Li C, Li X, Zhao B, Wang C (2020a) Exosomes derived from miR-544-modified mesenchymal stem cells promote recovery after spinal cord injury. Arch Physiol Biochem 126:369-375.

Li G, Fan ZK, Gu GF, Jia ZQ, Zhang QQ, Dai JY, He SS (2020b) Epidural spinal cord stimulation promotes motor functional recovery by enhancing oligodendrocyte survival and differentiation and by protecting myelin after spinal cord injury in rats. Neurosci Bull 36:372-384.

Li L, Li L, Zhang Y, Mu J, Chen J, Zhang C, Cao H, Gao J, Gao J (2020c) Transplantation of human mesenchymal stem-cell-derived exosomes immobilized in an adhesive hydrogel for effective treatment of spinal cord injury. Nano Lett 20:4298-4305.

Li X, Liu D, Xiao Z, Zhao Y, Han S, Chen B, Dai J (2019) Scaffold-facilitated locomotor improvement post complete spinal cord injury: Motor axon regeneration versus endogenous neuronal relay formation. Biomaterials 197:20-31.

Liu W, Rong Y, Wang J, Zhou Z, Ge X, Ji C, Jiang D, Gong F, Li L, Chen J, Zhao S, Kong F, Gu C, Fan J, Cai W (2020a) Exosome-shuttled miR-216a-5p from hypoxic preconditioned mesenchymal stem cells repair traumatic spinal cord injury by shifting microglial M1/M2 polarization. J Neuroinflammation 17:47.

Liu W, Xu B, Xue W, Yang B, Fan Y, Chen B, Xiao Z, Xue X, Sun Z, Shu M, Zhang Q, Shi Y, Zhao Y, Dai J (2020b) A functional scaffold to promote the migration and neuronal differentiation of neural stem/progenitor cells for spinal cord injury repair. Biomaterials 243:119941.

Luo Y, Xu T, Liu W, Rong Y, Wang J, Fan J, Yin G, Cai W (2020) Exosomes derived from GIT1-overexpressing bone marrow mesenchymal stem cells promote traumatic spinal cord injury recovery in a rat model. Int J Neurosci:1-13.

Ma D, Zhao Y, Huang L, Xiao Z, Chen B, Shi Y, Shen H, Dai J (2020) A novel hydrogel-based treatment for complete transection spinal cord injury repair is driven by microglia/macrophages repopulation. Biomaterials 237:119830.

Madaghiele M, Sannino A, Yannas IV, Spector M (2008) Collagen-based matrices with axially oriented pores. J Biomed Mater Res A 85:757-767.

Martirosyan NL, Kalani MYS, Bichard WD, Baaj AA, Fernando Gonzalez L, Preul MC, Theodore N (2015) Cerebrospinal fluid drainage and induced hypertension improve spinal cord perfusion after acute spinal cord injury in pigs. Neurosurgery 76:461-468.

Mehdar KM, Mahjri AA, Al Rashah AA, Alyazidi A (2019) Epidemiology of spinal cord injuries and their outcomes: a retrospective study at the King Khalid Hospital. Cureus 11:e6511.

Miller RH (1996) Oligodendrocyte origins. Trends Neurosci 19:92-96.

Mohammed R, Opara K, Lall R, Ojha U, Xiang J (2020) Evaluating the effectiveness of anti-Nogo treatment in spinal cord injuries. Neural Dev 15:1.

Murtaza M, Chacko A, Delbaz A, Reshamwala R, Rayfield A, McMonagle B, St John JA, Ekberg JAK (2019) Why are olfactory ensheathing cell tumors so rare? Cancer Cell Int 19:260.

National Spinal Cord Injury Statistical Center (2020) Spinal cord injury facts and figures at a glance. Natl Spinal Cord Inj Stat Cent Facts Fig a Glance. Birmingham, AL: University of Alabama at Birmingham

Qian K, Xu TY, Wang X, Ma T, Zhang KX, Yang K, Qian T Da, Shi J, Li LX, Wang Z (2020) Effects of neural stem cell transplantation on the motor function of rats with contusion spinal cord injuries: a meta-analysis. Neural Regen Res 15:748-758.

Reichelt AC, Hare DJ, Bussey TJ, Saksida LM (2019) Perineuronal nets: plasticity, protection, and therapeutic potential. Trends Neurosci 42:458-470.

Reshamwala R, Shah M, Belt L, Ekberg J, St John J (2020) Reliable cell purification and determination of cell purity: crucial aspects of olfactory ensheathing cell transplantation for spinal cord repair. Neural Regen Res 15:2016-2026.

Reshamwala R, Shah M, St John J, Ekberg J (2019) Survival and integration of transplanted olfactory ensheathing cells are crucial for spinal cord injury repair: insights from the last 10 years of animal model studies. Cell Transplant 28:132S-159S.

Shah M, Peterson C, Yilmaz E, Halalmeh DR, Moisi M (2020) Current advancements in the management of spinal cord injury: a comprehensive review of literature. Surg Neurol Int 11:1-7.

Shao M, Jin M, Xu S, Zheng C, Zhu W, Ma X, Lv F (2020) Exosomes from long noncoding RNA-Gm37494-ADSCs repair spinal cord injury via shifting microglial M1/M2 polarization. Inflammation 43:1536-1547.

Sharma KD, Pandanaboina SC, Srivatsan M, Xie JY (2020a) Predominant differentiation of rat fetal neural stem cells into functional oligodendrocytes in vitro. Neurosci Lett 736:135264.

Sharma KD, Schaal D, Kore RA, Hamzah RN, Pandanaboina SC, Hayar A, Griffin RJ, Srivatsan M, Reyna NS, Xie JY (2020b) Glioma-derived exosomes drive the differentiation of neural stem cells to astrocytes. PLoS One 15:e0234614.

Shimizu T, Kagawa T, Wada T, Muroyama Y, Takada S, Ikenaka K (2005) Wnt signaling controls the timing of oligodendrocyte development in the spinal cord. Dev Biol 282:397-410.

Silvestro S, Bramanti P, Trubiani O, Mazzon E (2020) Stem cells therapy for spinal cord injury: an overview of clinical trials. Int J Mol Sci 21:659.

Spilker MH, Yannas IV, Kostyk SK, Norregaard TV, Hsu HP, Spector M (2001) The effects of tubulation on healing and scar formation after transection of the adult rat spinal cord. Restor Neurol Neurosci 18:23-38.

Streuli C (1999) Extracellular matrix remodelling and cellular differentiation. Curr Opin Cell Biol 11:634-640.

Taccola G, Salazar BH, Apicella R, Hogan MK, Horner PJ, Sayenko D (2020) Selective antagonism of A1 adenosinergic receptors strengthens the neuromodulation of the sensorimotor network during epidural spinal stimulation. Front Syst Neurosci 14:44.

Tedeschi A, Dupraz S, Curcio M, Laskowski CJ, Schaffran B, Flynn KC, Santos TE, Stern S, Hilton BJ, Larson MJE, Gurniak CB, Witke W, Bradke F (2019) ADF/Cofilin-mediated actin turnover promotes axon regeneration in the adult CNS. Neuron 103:1073-1085.

Tetreault LA, Zhu MP, Wilson JR, Karadimas SK, Fehlings MG (2020) The impact of riluzole on neurobehavioral outcomes in preclinical models of traumatic and nontraumatic spinal cord injury: results from a systematic review of the literature. Glob Spine J 10:216-229.

Tkach M, Théry C (2016) Communication by extracellular vesicles: where we are and where we need to go. Cell 164:1226-1232.

Tran KA, Partyka PP, Jin Y, Bouyer J, Fischer I, Galie PA (2020) Vascularization of self-assembled peptide scaffolds for spinal cord injury repair. Acta Biomater 104:76-84.

Wang J, Chu R, Ni N, Nan G (2020) The effect of Matrigel as scaffold material for neural stem cell transplantation for treating spinal cord injury. Sci Rep 10:2576.

Wang J, Pearse DD (2015) Therapeutic hypothermia in spinal cord injury: the status of its use and open questions. Int J Mol Sci 16:16848-16879.

Wetts R, Fraser SE (1988) Multipotent precursors can give rise to all major cell types of the frog retina. Science 239:1142-1145.

Willison AG, Smith S, Davies BM, Kotter MRN, Barnett SC (2020) A scoping review of trials for cell-based therapies in human spinal cord injury. Spinal Cord 58:844-856.

Wright AA, Todorovic M, Murtaza M, St John JA, Ekberg JA (2020) Macrophage migration inhibitory factor and its binding partner HTRA1 are expressed by olfactory ensheathing cells. Mol Cell Neurosci 102:103450.

Xiao WP, Ding LLQ, Min YJ, Yang HY, Yao HH, Sun J, Zhou X, Zeng XB, Yu W (2019) Electroacupuncture promoting axonal regeneration in spinal cord injury rats via suppression of nogo/ngr and rho/ROCK signaling pathway. Neuropsychiatr Dis Treat 15:3429-3442.

Yang B, Zhang F, Cheng F, Ying L, Wang C, Shi K, Wang J, Xia K, Gong Z, Huang X, Yu C, Li F, Liang C, Chen Q (2020) Strategies and prospects of effective neural circuits reconstruction after spinal cord injury. Cell Death Dis 11:439.

Yousefifard M, Rahimi-Movaghar V, Nasirinezhad F, Baikpour M, Safari S, Saadat S, Moghadas Jafari A, Asady H, Razavi Tousi SMT, Hosseini M (2016) Neural stem/progenitor cell transplantation for spinal cord injury treatment; A systematic review and meta-analysis. Neuroscience 322:377-397.

Yue Y, Xue Q, Yang J, Li X, Mi Z, Zhao G, Zhang L (2020) Wnt-activated olfactory ensheathing cells stimulate neural stem cell proliferation and neuronal differentiation. Brain Res 1735:146726.

Zhang J, Cheng T, Chen Y, Gao F, Guan F, Yao M (2020a) A chitosan-based thermosensitive scaffold loaded with bone marrow-derived mesenchymal stem cells promotes motor function recovery in spinal cord injured mice. Biomed Mater 15:035020.

Zhang L, Zhuang X, Chen Y, Xia H (2019) Intravenous transplantation of olfactory bulb ensheathing cells for a spinal cord hemisection injury rat model. Cell Transplant 28:1585-1602.

Zhang Y, Wang WT, Gong CR, Li C, Shi M (2020b) Combination of olfactory ensheathing cells and human umbilical cord mesenchymal stem cell-derived exosomes promotes sciatic nerve regeneration. Neural Regen Res 15:1903-1911.

Zheng Y, Mao YR, Yuan TF, Xu DS, Cheng LM (2020) Multimodal treatment for spinal cord injury: A sword of neuroregeneration upon neuromodulation. Neural Regen Res 15:1437-1450.

Zhong D, Cao Y, Li CJ, Li M, Rong ZJ, Jiang L, Guo Z, Lu H Bin, Hu JZ (2020a) Highlight article: Neural stem cell-derived exosomes facilitate spinal cord functional recovery after injury by promoting angiogenesis. Exp Biol Med 245:54-65.

Zhong J, Xu J, Lu S, Wang Z, Zheng Y, Tang Q, Zhu J, Zhu T (2020b) A prevascularization strategy using novel fibrous porous silk scaffolds for tissue regeneration in mice with spinal cord injury. Stem Cells Dev 29:615-624.

Zhu S, Chen M, Deng L, Zhang J, Ni W, Wang X, Yao F, Li X, Xu H, Xu J, Xiao J (2020) The repair and autophagy mechanisms of hypoxia-regulated bFGF-modified primary embryonic neural stem cells in spinal cord injury. Stem Cells Transl Med 9:603-619.