Journal of Biosciences and Medicines, 2025, 13(1), 102-131
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Advancements in Stem Cell Therapeutics for Spinal Cord Injury: Theories and Applications

Pingping Mi[1*], Yanjie Zhong[1*], Yao Xu[2], Xingle Qin[3#]

[1]Graduate School, Youjiang Medical University for Nationalities, Baise, China
[2]Health Science Center, Ningbo University, Ningbo, China
[3]Department of Rehabilitation Medicine, Liuzhou People's Hospital, Liuzhou, China
Email: [#]1215809176@qq.com

How to cite this paper: Mi, P.P., Zhong, Y.J., Xu, Y. and Qin, X.L. (2025) Advancements in Stem Cell Therapeutics for Spinal Cord Injury: Theories and Applications. *Journal of Biosciences and Medicines*, **13**, 102-131.
https://doi.org/10.4236/jbm.2025.131010

Received: December 2, 2024
Accepted: January 13, 2025
Published: January 16, 2025

Abstract

One serious lesion to the central nervous system is spinal cord injury (SCI). Due to its intricate pathophysiological mechanisms and the irreparability of nerve cells, conventional rehabilitation approaches often prove inadequate for achieving full recovery. Consequently, most patients can only enhance their capacity for self-care in daily activities through early and proactive rehabilitation interventions. Stem cells are a class of cells that have the capacity to differentiate and are capable of safely and effectively differentiating into various types of neurons to repair or compensate for damaged cells, thereby exerting therapeutic effects. Currently, research on stem cell-based therapeutics for SCI is actively progressing and has yielded promising results. We discussed the anatomy, pathophysiological, the potential mechanisms of traditional therapy and stem cell therapy for SCI. The types of stem cells commonly used in current research and the latest progress in spinal cord therapy are described. Hope to serve as a resource for the use of stem cells in clinical settings.

Keywords

Stem Cells, Treatment, Mechanism, Spinal Cord Injury

1. Introduction

Spinal cord injury (SCI) is a severe neurological disorder, causing varying degrees of impairment in motor, sensory, and autonomic nervous functions and constitutes one of the most challenging neurological injuries in clinical treatment [1]. The etiological factors commonly associated with SCI include traumatic, pharmacological, infectious, neoplastic, and congenital origins. Among these, Traumatic

*First authors.
[#]Corresponding author.

spinal cord injury (TSCI) is the most common type of SCI, which includes injuries resulting from traffic accidents, falls from elevated surfaces, and other forms of trauma [2]. Subsequently to the occurrence of SCI, additionally to the immediate harm done to the tissue of the spinal cord, a cascade of secondary injuries, including inflammation, edema, and necrosis—that ensue post-injury will further exacerbate SCI [3]. SCI not only impairs the physical health of patients, imposes a heavy psychological burden on them, but also reduces their quality of life. Additionally, the high medical costs following SCI constitute a significant financial burden for patients' families [4]. According to incomplete statistics, the prevalence of spinal cord injuries is currently between 236 and 4178 cases per million people worldwide, and has manifested a notable upward trend in recent years [5]. The majority of individuals with SCI are unable to achieve complete recovery. An analysis of the data related to SCI revealed that less than one-third of the patients demonstrated functional improvement after treatment [6]. Patients with SCI typically require an extended hospital stay for comprehensive rehabilitation training and specialized nursing to attain a specific degree of functional recovery [5]. Nonetheless, the extent of functional recovery remains significantly limited, and the prognosis for elderly patients with comorbidities such as diabetes, cardiovascular and cerebrovascular diseases, and cognitive impairment is even more difficult. Consequently, the pursuit of more effective therapeutic strategies for SCI presents a considerable challenge for clinical traits. Due to the non-regenerative characteristics of nerve cells, current primary therapeutic strategies for SCI focus on mitigating secondary injuries, including high-dose steroid pulse therapy and early surgical decompression. The mechanism underlying high-dose steroid pulse therapy is likely linked to its anti-inflammatory effects at the injury site, and surgical decompression keeps the damaged spinal cord from experiencing additional compression [7] [8]. Nevertheless, these therapeutic strategies do not achieve the restoration of neural functions. Surgical decompression is presently considered relatively safe. Early surgical intervention for SCI patients is increasingly becoming standard practice, however, the evidence supporting its efficacy remains notably limited [7]. Under certain triggered conditions, stem cells are a type of cell that has the capacity to develop into other cell types. Consequently, the multipotent differentiation capacity of stem cells suggests their potential application in generating various cell types and tissues, including neurons. This capability may allow the damaged spinal cord tissue repair, hence permitting the restoration of spinal cord [7]. This article highlights the most recent developments in stem cell transplantation for spinal cord injury while also examining the therapeutic options currently used to treat the condition, concentrating especially on mesenchymal stem cells in this situation. This paper analyzes the progress in stem cell therapy research, intending to provide scientific and rational guidance for the treatment of spinal cord injury patients and future related scientific investigations.

2. Pathophysiology of Spinal Cord Injury

The spinal cord is the tissue inside the spinal canal that consists of two major parts,

gray matter and white matter. The structure houses the cell bodies of neurons, along with ascending and descending fibers that transmit sensory, motor, and autonomic nervous information [9]. The normal physiological functions of the spinal cord involve interactions among different cell types, including neurons, microglia, astrocytes, and oligodendrocytes. Following SCI, these cell interactions are disrupted, rendering the recovery of spinal cord function more challenging [3] [10]. There exist numerous causes of SCI, yet their pathophysiological mechanisms are similar in cases of SCI [11]. SCI can be classified into two stages based on pathophysiological changes: primary injury and secondary injury. Acute, subacute, and chronic stages of secondary damage can be distinguished based on the progression of the condition. Different stages exhibited diverse characteristics, encompassing a number of pathological alterations including inflammation, ischemia, and apoptosis [12] [13].

2.1. Primary Injury

Primary injuries are predominantly mechanical in nature, such as spinal cord contusions resulting from spinal displacement following trauma, as well as compression and laceration. Among them, spinal cord compression constitutes the most prevalent etiology of SCI, which may result in harm to the blood-spinal cord barrier (BSCB) and local capillaries [14] [15]. The BSCB serves as a crucial protective structure t that preserves the spinal cord microenvironment's integrity against both endogenous and exogenous influences, and dysfunction of the BSCB can give rise to edema and subsequent secondary neural injury [16] [17]. Neurogenic shock resulting from SCI can lead to hypotension. Given that systemic blood pressure and perfusion pressure are directly correlated, this condition results in reduced perfusion of the injured spinal cord and influenced local microcirculation, hindering the delivery of essential nutrients and oxygen to neural tissue, thereby preventing improvement in spinal cord function [18] [19].

2.2. Secondary Injury

This phase may manifest within hours to days following the onset of primary injury, involving changes such as ischemia, edema, and inflammatory cell infiltration, ultimately leading to irreversible processes including neuronal apoptosis, necrosis, axonal degeneration, demyelination, and glial scar formation [20]. The following section provides a detailed description of the pathophysiological changes occurring during the secondary injury stage.

2.2.1. Ischemia and Edema of the Spinal Cord

Following the initial injury, the vascular supply to the spinal cord is impaired, resulting in ischemia [21]. Cellular edema occurs as the consequence of ischemia. The main cause of ionic edema development is the blood-spinal cord barrier's enhanced permeability, causes ions and water to escape from the interstitial space [3] [22]. The cell membrane's pore size increases as a result of endothelial damage and inflammation, thereby allowing large plasma-derived molecules to permeate

the membrane. Vasogenic edema is the result of this imbalance between intracellular solutes and water input [23].

2.2.2. Immune Response Following SCI

Through the compromised blood-spinal cord barrier, hematogenous immune cells such as neutrophils, mononuclear macrophages, and lymphocytes infiltrate the spinal cord tissue [20]. These cells secrete pro-inflammatory or immunoregulatory factors that are essential to the immune response. Local inflammatory responses following SCI encompass a diverse array of cell types, such as microglia, astrocytes, and dendritic cells. Peripheral immune cell populations, including macrophages and neutrophils, which are vital in the development of inflammation following spinal cord injury (SCI). Subsequently, an intensified inflammatory response is caused by the release of pro-inflammatory cytokines (TNF-α, IL-1, IL-6, and IL-10) and the increase of inflammatory mediators (leukotrienes, bradykinin, and prostaglandins) [24]. Furthermore, the downregulation of miR-96 following SCI serves as a key element in the exacerbation of the inflammatory response [25]. After SCI, a stable and persistent inflammatory response can significantly impede tissue repair, regeneration, and the restoration of neural function [26]. Recent investigations have established inflammation as a crucial component impacting secondary injury severity [27], and the subsequent section will concentrate on the immune cells previously discussed.

2.2.3. The Mechanisms of Immune Cells Mediated Inflammatory Response

Microglia: Microglia exhibit physiological roles analogous to those of macrophages in the brain and spinal cord, acting as the central nervous system's (CNS) primary and most crucial line of defense in the immune response. An increasing number of studies are demonstrating that microglia might be important target cells for SCI-related neural repair [28] [29]. There are mainly two phenotypes of microglia, and their phenotypic transformation is mainly dependent on the local microenvironment. The M1 phenotype primarily increases inflammatory reactions and exacerbates neuroinflammation; conversely, the M2 phenotype has anti-inflammatory properties locally and facilitates tissue repair [30]. Therefore, effectively inducing microglial polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype while releasing cytokines that reduce inflammation to modify the inflammatory microenvironment can mitigate inflammatory responses and reduce secondary injuries [31]. Shuhei Kobashi *et al.* established mouse models of SCI and subsequently injected M1 and M2 microglia, induced by interleukin (IL)-4 or granulocyte macrophage colony-stimulating factor (GM-CSF), into the spinal canals of these SCI mice. Their findings indicate that early on following a spinal cord injury, microglia can mitigate immune cell infiltration within the injured spinal tissue and reduce apoptosis of adjacent neuronal cells and oligodendrocytes, thereby enhancing the stability of the damaged spinal cord. Notably, axonal transport was improved to varying extents in both M1- and

M2-treated groups; however, recovery of motor function was significantly superior in those receiving M2 treatment compared to those treated with M1. This contrasts with the traditionally accepted perspective that the M1 phenotype promotes inflammation, as it also possesses beneficial properties. This study revealed that M2 macrophages exhibit reduced capabilities in migration and phagocytosis compared to M1 microglia. Furthermore, in the context of SCI, could contribute to while the therapeutic effects are probably mediated via the collaborative actions of both M2 and M1 microglia [32]. Additionally, prior investigations have established connections between microglial polarization/inflammatory responses with Nrf2/HO-1 signaling pathways [33]; specifically, Nrf2 acts as a cytoprotective factor capable of activating downstream HO-1 gene expression upon inflammatory stimuli while concurrently inhibiting inflammation via nuclear transcription factor (NF-κB) signaling [34].

Astrocytes: The glial scar formation is a reactive mechanism of cells. Neuron are non-regenerative, and thus the nervous system's recovery is primarily led by astrocytes [35] [36]. In the initial seven days after a spinal cord injury, astrocytes are activated. The fundamental process may entail the release of specific cytokines, such as TNF, from damaged spinal cord tissue, which bind to gp130 receptors. This interaction subsequently activates the STAT3-a1ACT signaling axis through phosphorylation of Janus kinase (JAK) [37]. Astrocytes can be categorized into two distinct types: A1 and A2. The A1 subtype demonstrates neurotoxic properties and is associated with the promotion of inflammation, whereas the A2 subtype facilitates axon regeneration and confers neuroprotection [38] [39]. The formation of astrocytic scars serves a dual purpose in the context of SCI: it mitigates inflammation and confines the lesion area, while simultaneously, growth-inhibitory molecules including semaphorin 3A and chondroitin sulfate proteoglycans (CSPGs) are secreted by the astrocytes in these scars. This secretion hinders neuronal and axonal repair and regeneration, ultimately complicating the recovery of motor and sensory functions [40] [41]. Changnan Xie *et al.* found that conditional astrocyte YAP knockout in astrocytes of SCI mice inhibited glial scar formation. Conversely, activation of the YAP signaling pathway promoted astrocyte proliferation. This study elucidates that the mechanism underlying astrocyte proliferation following SCI may involve significant upregulation of bFGF mRNA, its binding to the FGF receptor, and subsequent activation of YAP via the RhoA pathway. Ultimately, YAP enhances astrocyte proliferation by negatively regulating CRM1-mediated nuclear distribution of p27Kip1, thereby facilitating glial scar formation [42]. In addition to the previously mentioned pathways, following spinal cord injury (SCI), G protein-coupled receptors and receptor tyrosine kinases on the cell membrane activate phosphatidylinositol 3-kinase (PI3K), which subsequently makes the serine residue at position 473 (Ser473) and the threonine residue at position 308 (Thr308) on AKT phosphorylated. At this stage, AKT becomes activated. Furthermore, mTORC2 facilitates maximal activation of AKT, ultimately promoting astrocyte proliferation [43] [44]. In summary, astrocytes can promote

their proliferation through the previously mentioned YAP pathway (bFGFRhoA-YAP-p27Kip1) and the PI3K/AKT signaling pathway. Ultimately, reactive astrocytes use the integrin-cadherin pathway to engage with type I collagen and aid in the creation of glial scars [45] [46].

Neutrophil: Previous studies have indicated that neutrophils are detrimental to the pathophysiological changes associated with SCI. The primary reasons for this can be summarized as follows: Firstly, by releasing pro-inflammatory mediators such as proteolytic enzymes, lysosomal enzymes, and reactive oxygen species (ROS), activate other immune cells and glial cells, thereby intensifying the inflammatory cascade and exacerbating tissue damage [47]-[49]. Secondly, Through the promotion of neuroinflammation and the disruption of the blood-spinal cord barrier, neutrophils create neutrophil extracellular traps (NETs), which further exacerbate secondary damage [50] [51]. However, an increasing amount of study in the last few years has demonstrated that neutrophils can also exert beneficial effects. Investigators have identified a novel subpopulation of neutrophils: $CD14^{+}Ly6G^{low}$ granulocytes. Following the onset of inflammation, the active component in zymosan with regenerative properties—β-1,3-glucan, can activate $Ly6G^{low}$ neutrophils. Upon activation, these neutrophils promote axonal regeneration and protect damaged neurons by growth factors like NGF and IGF-1 being secreted. However, when researchers administered anti-NGF and anti-IGF-1 antibodies to the experimental mice, the ability of $CD14^{+}Ly6G^{low}$ neutrophils to facilitate axonal regeneration was not entirely abolished. This suggests that additional growth factors may be involved in this process, warranting further investigation [52] [53]. Stirling *et al.* utilized an antibody targeting the lymphocyte antigen 6 complex locus (Ly6G) to treat mice with moderate T9/10 contusion injuries. Employing advanced imaging techniques, they successfully visualized neutrophil recruitment at the injury site for the first time. Their findings revealed a 90% reduction in neutrophil numbers following the forementioned antibody treatment, whereas monocytes and lymphocytes showed no discernible alterations. Notably, this decrease in neutrophil levels exacerbated spinal cord injury in the mice, as the absence of neutrophils resulted in diminished levels of several growth factors, including FGFs and VEGF, thereby downregulating the regenerative environment of the injured spinal cord post-SCI. These results underscore that neutrophils play a beneficial role following spinal cord injury [54]. Furthermore, the early infiltration of neutrophils can accurately orchestrate the aggregation of macrophages through the secretion of enzymes and other factors, thereby creating an environment conducive to phagocytosis by macrophages [55].

Bone marrow-derived macrophages: There are two different kinds of macrophages: M1 and M2. The main characteristics of the M1 phenotype are harmful and pro-inflammatory effects. In contrast, the M2 phenotype generates anti-inflammatory substances, and predominantly exhibits beneficial roles, including neuroprotection and facilitation of nerve regeneration [56]. Unexpectedly, prior research has demonstrated that macrophages in the injured tissue following SCI

are primarily inclined to the M1 phenotype [57]. Antje Kroner *et al.* developed a spinal cord contusion mouse model to assess the expression of several M1 and M2 markers in adult mice's spinal cord macrophages 15 days after spinal cord damage. They found that the MAP kinase-activated protein kinase 2 (MK2) may influence the pro-inflammatory processes of macrophages in SCI, leading to an increase in TNF expression. Furthermore, iron can also induce elevated TNF expression, ultimately resulting in the macrophages in the wounded tissue to eventually polarize toward the M1 phenotype and aiding in the transformation of M2 macrophages into their functional state [58]. In another study, it was revealed that myelin debris produced locally following spinal cord injury (SCI) is regulated by the endogenous glucocorticoid receptor (GRs) signaling pathway, which mediates the phagocytosis of myelin and induces phenotypic alterations in M2 macrophages, ultimately resulting in the formation of foam macrophages. This process contributes to the persistence of chronic inflammation and increases harm to the spinal cord injury [56] [59]. Furthermore, according to current research, the lipid catabolism pathway may be another critical mechanism for regulating macrophage polarization and phenotype [60]. The findings from these investigations provide potential therapeutic targets for promoting M2 polarization in future interventions.

2.2.4. Neurotransmitters Also Exert an Influence on the Development of Secondary Injury Following SCI

After SCI, Excitatory amino acid levels, including those of glutamate and aspartate, are observed to be elevated. In the central nervous system, glutamate is an excitatory neurotransmitter. Nevertheless, excitotoxicity, oxidative damage, and calcium-dependent nitric oxide production can be caused by excessive glutamate levels, which collectively contribute to secondary SCI [46]. Following the occurrence of secondary injury, the exacerbated damage caused by free radicals and lipid peroxidation within the cell membrane—coupled with a series of signaling events associated with secondary injury in the affected tissue, ultimately culminates in neuronal death [61]. As acute secondary injuries persist and transition into the subacute phase, axonal demyelination, Wallerian degeneration, neuronal apoptosis, and the development of fibrotic glial scars are the hallmarks of this stage. [62]. After SCI, at the chronic stage of secondary injury, the established glial scar undergoes further maturation, accompanied by changes such as cyst formation and axonal degeneration [63]. Given that primary SCI is inherently unpredictable and irreversible, subsequent secondary injuries frequently account for permanent loss of motor function, sensory perception, and other neurological capabilities following SCI. Consequently, an increasing number of researchers are focusing on targeting secondary injury as a therapeutic intervention during this critical regulatory period.

3. Therapeutic Method

Surgical intervention, medication management, treatment for rehabilitation and

nursing care are currently the main clinical treatment techniques for spinal cord injury (SCI). During the acute stage of therapy, the focus is on stabilizing the patient's condition and taking life-saving measures. In the chronic phase, the principal objectives are to restore functional capabilities, prevent complications. Furthermore, during the therapeutic process, patients exhibiting symptoms of low mood, depression or suicidal ideation may necessitate psychological intervention or support from a mental health professional [64].

3.1. Medicine Treatment

In previous drug treatments during the acute phase, corticosteroids have been recognized as the standard therapeutic intervention throughout TSCI's acute phase. Methylprednisolone (MP) was previously the only FDA-approved pharmaceutical product used to treat spinal cord injury. Its mechanism of action primarily involves enhancing spinal cord blood supply, repairing the blood-spinal cord barrier's integrity, scavenging excessive reactive oxygen species, mitigating secondary inflammatory infiltration, and promoting the secretion of neurotrophic factors [20]. However, a considerable amount of clinical evidence indicates that high dosages of MP are linked to negative side effects, such as gastrointestinal bleeding and respiratory tract infections, which may ultimately result in mortality [65] [66]. Due to the limited evidence supporting its precise therapeutic efficacy and the prevalence of various adverse effects, corticosteroids have largely been discontinued in most treatment protocols for spinal cord injuries. One class of pharmaceutical medicines is represented by nonsteroidal anti-inflammatory medications (NSAIDs) that achieve their anti-inflammatory effects primarily via cyclooxygenase (COX) inhibition. In the realm of pharmacological interventions for SCI, NSAIDs are acknowledged as effective agents in mitigating inflammation and edema within the spinal cord [67]. Research employing rat models of spinal cord contusion has revealed that the damaged spinal tissue has a markedly elevated expression of COX-2. COX-2 inhibition has been demonstrated to improve motor function [68], potentially through the suppression of Rho-A signaling [67]. Due to the current lack of publicly available guidelines on the safe and effective dosing of nonsteroidal anti-inflammatory drugs for acute SCI, coupled with the absence of definitive clinical trials demonstrating their therapeutic efficacy, these agents are not routinely employed in clinical practice despite their potential benefits in treating spinal cord injury. Furthermore, researchers have identified a variety of potential pharmacological candidates targeting the pathophysiological mechanisms underlying SCI, including naloxone, minocycline, riluzole, magnesium, gabapentin, and GM-1 ganglioside [14] [69] [70]. However, these agents remain confined to preclinical studies or theoretical frameworks at present, and drug-based therapeutic strategies for functional recovery in chronic SCI continue to be limited.

3.2. Surgical Therapy

During the severe stage of SCI, the primary aim of surgical intervention is to

achieve decompression and restore spinal stability. The question of whether early surgical intervention is warranted for SCI patients has been a subject of ongoing debate among researchers and clinical practitioners. Patients who had decompression surgery within 24 hours had a significantly higher rate of two-level improvement in the American Spinal Injury Association (ASIA) impairment scale than those who had delayed decompression surgery, according to the findings of a 6-month follow-up study on patients who had surgical intervention after SCI [71]. However, some critics argue that because the timing of surgical decompression was not determined randomly, there may be significant subjective bias in selecting candidates for early surgery by surgeons. Despite these critiques concerning subjectivity and research design, numerous studies evaluating the timing of surgical decompression have indicated that early intervention can mitigate neurological damage, enhance prognosis, and reduce complications [72]-[74].

3.3. Rehabilitation Therapy

Despite the significantly low rate of motor, sensory, and autonomic function recovery after SCI, numerous clinical cases have indicated that patients who initiate rehabilitation exercises promptly after the stabilization of vital signs exhibit improved prognoses and significantly fewer complications. Typically, rehabilitation interventions for SCI encompass limb functional training, physical therapy, repetitive transcranial magnetic stimulation, and hyperbaric oxygen (HBO) therapy [75]. The potential mechanisms underlying HBO include a reduction in cellular apoptosis as well as a decrease in inflammation and edema. Increased oxygen tension in the spinal cord during HBO treatment may lessen spinal cord ischemia damage and improve clinical results [76]. Furthermore, timely rehabilitative care is essential for preventing complications like pneumonia, pressure ulcers, and deep vein thrombosis [75].

3.4. Stem Cell Therapy

While notable advancements have been achieved in surgical interventions, pharmacological treatments, and rehabilitation, their efficacy in addressing motor and sensory dysfunctions following SCI remains markedly limited. Currently, no therapeutic intervention has demonstrated the ability to significantly mitigate the severe long-term sequelae associated with SCI [77]. In 2001, Orlic *et al.* simulated coronary heart disease by ligating the coronary artery in mice and then giving the left ventricle of the experimental subjects a direct injection of bone marrow stem cells. According to their research, the c-kit/SCF (stem cell factor) signaling pathway could allow the injected bone marrow stem cells to move to the damaged location, facilitating myocardial regeneration, ultimately leading to a reduction in infarct size and an improvement in cardiac hemodynamics [78]. This study is the first to show that necrotic cardiac tissue can be replaced by bone marrow stem cells, and facilitate cardiomyocyte regeneration, thereby challenging the prevailing notion that stem cell functions are restricted to the specific cell types of their

originating organs. However, at that time, it remained unclear whether adult cardiac cells produced SCF. Consequently, the effectiveness of bone marrow stem cell transplantation as a treatment for coronary heart disease patients. Nevertheless, these findings have instilled new optimism for a variety of refractory diseases. Consequently, the use of stem cell therapy in treatment regimens for different organ ailments has grown. In the previous few years, Stem cells have been used in a number of fundamental and clinical investigations to treat spinal cord injuries. Numerous preclinical animal studies and several phase III clinical trials have reported partial improvements in sensory and motor functions associated with SCI [79] [80]. Currently, it is generally accepted that stem cells' therapeutic effects mainly appear in three important areas. Firstly, stem cells exhibit multi-differentiation potential, which is essential for the replacement of degenerative and necrotic cells. Secondly, the damaged microenvironment's inflammatory reactions are lessened by the anti-inflammatory substances secreted by these cells. Lastly, a wide range of cytokines, growth factors, and cell adhesion molecules that are necessary for enhancing the microenvironment and facilitating tissue regeneration are secreted by stem cells [81] [82].

Three main types of stem cells can be distinguished based on their developmental stage: induced pluripotent stem cells, adult stem cells, and embryonic stem cells (ESCs). Mesenchymal stem cells (MSCs), neural stem cells (NSCs/NPCs), induced pluripotent stem cells (iPSCs), olfactory ensheathing glial cells (OECs), hematopoietic stem cells, and skin-derived progenitor cells are some of the other subtypes of adult stem cells [20]. In contemporary research, a variety of stem cell types are available for cell transplantation, each exhibiting distinct advantages and disadvantages. Because of their advantageous characteristics, MSCs have emerged as a prominent candidate in regenerative medicine preclinical and clinical research. These include ease of accessibility, extensive biological effects, minimal ethical concerns, and low immunogenicity [83]. The following sections will offer a detailed analysis of the commonly employed stem cell types in contemporary research, with a specific focus on the progress achieved in the study of mesenchymal stem cells.

3.4.1. ESCs

ESCs were initially isolated and grown from mice in 1981, showing an exceptional capacity to differentiate into any sort of cell [84]. ESCs can develop into neurons and glial cells in the context of SCI, thereby substituting dysfunctional cells or tissues [85]. Prior research has demonstrated that the transplantation of ESCs is effective in facilitating recovery after SCI. However, the use of ESC transplantation raises concerns regarding teratoma formation, immune rejection, and ethical dilemmas associated with embryo destruction [86].

3.4.2. iPSCs

Cellular reprogramming or adult somatic cells can be used to create IPSCs, thereby circumventing associated ethical concerns; however, they carry a risk of

tumorigenesis. A growing body of research has substantiated the potential for treating SCI via iPSC transplantation [87]. For instance, Nori *et al.* showed that human iPSC-derived cells could survive and differentiate into neurons, astrocytes, and oligodendrocytes when they were implanted into NOD/SCID mice. In the mice, functional recovery was shown, and subsequent tracking revealed no tumor formation [88]. A contusive SCI model was developed by Kobayashi *et al.* in macaques and transplanted hipsc-derived neural progenitor cells (npc) to the lesion site. The study revealed that the transplanted cells were capable of secreting neurotrophic factors including CNTF and VEGF, and new blood vessels emerged at the lesion site. In addition, hiPSC-NS/PCs can prevent the injury center from demyelinating and enhance axon regeneration, thus promoting functional recovery after spinal cord injury [89]. Although iPSCs may lead to teratoma formation, their pluripotency and beneficial effects in SCI warrant future investigations aimed at developing transplantation strategies that minimize teratogenic risks while maximizing the therapeutic potential of iPSCs. Encouragingly, recent studies have indicated that immunosuppressants may possess the ability to mitigate the tumorigenic potential associated with iPSCs [90].

3.4.3. NS/PCs

Multipotent cell types known as NSCs and NPCs have been isolated from the ependymal layer around the spinal cord's central canal, the hippocampal region, and the subventricular zone of the lateral ventricles [91]-[93]. NSCs have the innate capacity to produce several kinds of brain cells and can be obtained from a range of source. The mechanism by which NSCs exert their effects involves releasing pro-regenerative factors and replacing lost neural cells in SCI, as well as neurotrophic factors, to protect damaged tissue. Consequently, following SCI, Neural stem cell transplantation can facilitate the replacement of injured cells such as neurons, oligodendrocytes, and astrocytes. Currently, there is a growing body of research focused on this form of cell transplantation [94] [95]. In rats suffering from SCI, Ziqian Ma *et al.* showed that epidermal neural crest stem cells (EPI-NCSC) could activate the PI3K/AKT signaling pathway, preventing neuronal death and providing a neuroprotective effect. The results reflect the therapeutic role of this pathway in SCI, but more studies are needed to fully elucidate the underlying molecular mechanisms [96]. Rosenzweig *et al.* established an SCI model in rhesus monkeys, proving that NPCs were transplanted lived and developed into neurons and astrocytes, allowing for functional recovery [97].

3.4.4. MSCs

Multipotent cells called mesenchymal stem cells can be obtained from bone marrow, blood, or other dermal tissues. They are a subset of adult stem cells with the ability to develop into a variety of cell types, such as adipocytes, myocytes, chondrocytes, and osteoblasts [98] [99]. In comparison to other types of stem cells, MSCs have a number of benefits over other kinds of stem cells, including: 1) They can be readily isolated and stored and come from a variety of sources; 2) the risk

of teratoma formation is significantly lower than that associated with iPSCs or ESCs; 3) they are not subject to ethical constraints [100] [101]. According to a case study on the application of combination therapy based on mesenchymal stem cells for chronic SCI, this approach is both safe and effective, with a majority of patients demonstrating varying degrees of motor and sensory function recovery [102]. The limitation of MSCs relative to iPSCs and ESCs is their comparatively lower reproducibility. MSCs may affect SCI through a variety of possible methods, including the paracrine release of anti-inflammatory cytokines and neurotrophic factors, angiogenesis promotion, and decreased glial scar formation [103] [104]. T Brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), glial cell line-derived neurotrophic factor (GDNF), insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF) are the main neurotrophic factors released by mesenchymal stem cells [105] [106]. These neurotrophic factors are essential for shielding injured neurons, promoting their survival, facilitating axon regeneration, and enhancing angiogenesis [107]. For example, nerve growth factor (NGF) primarily interacts with the TrkA and p75NTR receptors to activate intracellular signaling pathways. Similarly, the TrkB receptor is primarily activated by brain-derived neurotrophic factor (BDNF), which starts downstream signaling cascades that include the MAPK/ERK and PI3K/Akt pathways [108] [109].

In the realm of immune regulation, MSCs are essential for immune modulation because they secrete growth factors like interleukin 10 or transforming growth factor β1, which increase the synthesis of anti-inflammatory factors including TGF-β1, IL-1β, IL-6, and TNF-α [110]. Furthermore, MSCs facilitate macrophages change from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, thereby exerting immunoregulatory functions [111]. MSCs also engage directly with natural killer (NK) cells or upregulating CD73 expression on these cells to convert AMP into adenosine [112]. Additionally, MSCs mediate direct interactions with NK cells through TLR4 expression, which lowers the synthesis of cytokines that promote inflammation. Moreover, direct cell fusion is one way that mesenchymal stem cells can provide therapeutic effects [107] [113]. Currently, t bone marrow-derived mesenchymal stem cells (BMMSCs), adipose-derived mesenchymal stem cells (ADSCs), and umbilical cord-derived mesenchymal stem cells (UCMSCs) are the three main types of MSCs used in stem cell transplantation research. A comprehensive description will be provided in the subsequent chapter.

4. Mesenchymal Stem Cells in SCI Treatment

4.1. BMMSCs

Mercedes Zurita *et al.* carried out a study in which BMMSCs were administered via intramedullary injection to pigs with spinal cord injury. The results demonstrated that, after 12 weeks, The average score on the motor function evaluation

scale for the wounded pigs was 6.2, with some individuals even regaining the ability to stand independently. Moreover, histological analysis revealed the presence of neurons and astrocytes within the affected regions [114]. These findings provide compelling evidence for the potential of bone marrow-derived mesenchymal stem cells as a treatment in sophisticated mammalian models of spinal cord injury. Furthermore, research by Chizuka Ide *et al.* has demonstrated that transplantation of these stem cells significantly promotes axonal regeneration and tissue repair following SCI in rat models [115].

4.2. ADSCs

ADSCs are more abundant than their bone marrow counterparts and are notably more accessible, facilitating easier procurement and isolation. ADSCs have been shown to be both safe and beneficial, with applications in the transplantation for a variety of conditions, including cosmetic reconstruction surgeries, chronic ulcers associated with lower limb arterial diseases, and SCI. ADMSC transplantation's effectiveness has been confirmed in a number of central nervous system (CNS) injury models and is connected to the regulation of inflammatory. Adipose-derived mesenchymal stem cells may have therapeutic benefits for SCI mice by inhibiting the Jagged1/Notch signaling pathway, resulting in reduced phosphorylation of JAK/STAT3 in astrocytes and subsequent downregulation of inflammatory mediator post-SCI, according to Zhilai Zhou *et al.* These findings align with previously proposed mechanisms suggesting an anti-inflammatory function of ADSCs in the management of spinal cord injuries [116]. There was no indication of tumorigenicity or other unfavorable side effects in the preliminary research evaluating the safety profile of intravenous AD-MSC treatment. A study investigating autologous AD-MSC transplantation via intrathecal delivery involved 14 patients with spinal cord injury; following intervention, 10 patients demonstrated sensory improvement while MRI assessments revealed stable lesion sizes. Importantly, none experienced severe adverse events related to AD-MSC treatment [117]. Zhou *et al.*'s research further established that ADMSC transplantation can mitigate neuroinflammation, promote nerve tissue preservation, and ultimately enhance functional recovery in rats subjected to SCI [116]. Adipose-derived mesenchymal stem cells were delivered intrathecally to patients with traumatic SCI in a phase 1 experiment by Mohamad Bydon *et al.* observing that among 10 participants receiving this intervention, 7 exhibited improvements in their AIS grades compared to baseline measurements [118].

4.3. UCMSCs

UCMSCs exhibit superior in vitro expansion capabilities, a more rapid proliferation rate, and reduced immunogenicity compared to BM-MSCs [119]. However, their derivation from umbilical cord blood raises potential ethical concerns. Consequently, compared to the two mesenchymal stem cell types previously described, research on umbilical cord-derived mesenchymal stem cells (UC-MSCs)

has been comparatively limited. In a clinical trial investigating UC-MSC treatment for SCI, 22 patients received intrathecal injections of UC-MSCs; among these participants, 13 demonstrated improvements in motor function, sensory perception, and bladder voiding capabilities without any significant adverse reactions reported [120]. Importantly, regarding optimal timing for cell transplantation, numerous studies indicate that during the acute phase various inflammatory cell types can compromise transplanted stem cells' viability while glioma formation in chronic stages may inhibit axonal regeneration. As such, it is widely accepted that the subacute phase which lasts 10 - 14 days after the damage represents an ideal window for cell transplantation [121]. However, in this study, all selected patients were in the chronic stage of SCI. Nevertheless, they demonstrated improvements in motor and sensory functions following treatment. This research implies that the subacute period should not be the exclusive time frame for bone marrow mesenchymal stem cell transplantation following SCI—a significant advancement in determining time windows for future stem cell therapies.

In conclusion, mesenchymal stem cells, especially adipose-derived mesenchymal stem cells and bone marrow-derived stem cells, have been widely used in animal models of SCI research and show higher promise for the regenerative therapy of SCI than other types of stem cells. However, the efficacy of mesenchymal stem cell therapy for SCI remains a subject of debate [82]. Less than 1% of implanted mesenchymal stem cells move to the damaged tissue, according to certain research [122]. Reactive oxygen species production, inflammatory cell infiltration into the injured area, and disruptions in the local microenvironment may all be responsible for the transplanted stem cells' poor differentiation potential and low survival rate [123].

4.4. Paracrine Factors Secreted by Mesenchymal Stem Cells

In the last few years, building upon the foundation of mesenchymal stem cell transplantation, researchers have identified that MSC-secreted paracrine factors have a variety of advantageous properties, such as anti-inflammatory, anti-apoptotic, antioxidant properties, as well as promoting angiogenesis and neural regeneration [124] [125]. Investigations into these paracrine mechanisms have been actively pursued. Recent studies suggest that these effects are primarily mediated by exosomes (Exo) [126]. Compared to traditional cellular transplantation methods, this approach has attracted significant attention as an innovative cell-free therapeutic strategy for SCI [127]. Studies have shown that MSCS-EXOS has similar effects to MSCs, and has the advantages of stable existence in the blood circulation without being swallowed by the macrophage system, easy transfer and storage [128].

Adipose-derived mesenchymal stem cell exosomes (ADMSC-Exo) have been shown by Yi Luo *et al.* to activate the Nrf2/HO-1 pathway by reducing the expression of M1 microglia, increasing the expression of M2 microglia, and inhibiting inflammatory factors at the localized injury site after SCI. They demonstrated that

ADMSC-Exo not only lessens SCI but also helps rats regain their motor function by creating a rat model of the condition, corroborating findings from previous studies. However, this research has yet to elucidate the specific mechanisms underlying the Nrf2/HO-1 pathway; thus, understanding its complex mechanisms remains a challenge for future investigations [129]. Nine patients with full subacute spinal cord damage participated in a phase I clinical trial that showed no significant adverse effects after receiving intrathecal injections of allogeneic hUC-MSC exosomes, suggesting a good safety profile. Every individual showed differing levels of improvement in their motor and sensory abilities. This trial represents the first clinical data regarding the application of intrathecal allogeneic exosomes for the care of individuals with SCI. However, since this study primarily aimed to assess safety and involved a limited sample size, it could not adequately evaluate precise efficacy. Larger sample numbers in upcoming phase II/III clinical trials are necessary for additional efficacy evaluation [130]. Min Chen *et al.* were the first to demonstrate in a rat model of spinal cord injury that exosomes derived from bone marrow mesenchymal stem cells, which contain miR-26a-5p, can bind to the 3'-UTR of their target mRNA, leading to the downregulation of EZH2 expression, an increase in BDNF and TrkB levels, and the promotion of KCC2 transcription, thereby enhancing recovery from spinal cord injury [131]. IFN regulatory factor 5 (IRF-5) is an inflammatory factor that promotes differentiation of macrophages into the M1 phenotype. The exosome miRNA-125a derived from BMMSCs exerts its neuroprotective effect by regulating the expression of IRF-5 in spinal cord injury [132]. LinWang *et al.* found that the exosomes of MSCs have a powerful anti-inflammatory effect, which can inhibit the transformation of macrophages to M1 phenotype by reducing the expression of inflammatory factors such as TNF-α and NF-κB, and ultimately improve spinal cord function [133]. Furthermore, Azar Abbas *et al.* established a mouse model of SCI to show that iPSCs-derived exosomes containing miRNAs could promote neuroprotection and mitigate neuronal inflammation, thereby facilitating functional recovery post-SCI. In comparison to direct transplantation of iPSCs, exosome-based therapy exhibits lower immunogenicity and greater therapeutic efficacy. These findings suggest that the efficacy and safety of exosomes as an emerging therapeutic modality based on stem cell transplantation are not coincidental, indicating significant potential for future development [134].

5. Traditional Chinese Medical Therapy in China

Traditional Chinese medicine interventions, including acupuncture and herbal therapies such as triptolide, tanshinone, ginsenosides, genistein, and curcumin, have demonstrated the ability to facilitate the recovery of neurological function [135] [136].

5.1. Acupuncture

Research has demonstrated that tropomyosin can be activated by acupuncture via

the PI3K/Akt and ERK1/2 signaling pathways. This activation subsequently causes cyclic AMP (cAMP) to rise, resulting in the upregulation of BDNF gene transcription, thereby facilitating functional recovery. Furthermore, it has been shown that acupuncture can inhibit epidermal growth factor receptor activity, promote axon regeneration, and reduce glial scar formation [137] [138].

5.2. Herbal Therapies

Experiment studies have demonstrated that triptolide exerts anti-inflammatory effects and promotes spinal cord recovery by upregulating miR-96 expression, inhibiting TNF-α and IL-1β in microglia, and reducing the levels of intermediate filament proteins [139]. Dan Luo *et al.* found that sodium tanshinone IIA sulfonate (STS) can inhibit MMP activation, promote the synthesis of tight junction (TJ) and adherens junction (AJ) proteins, thereby decreasing the permeability of the damaged blood-spinal cord barrier (BSCB), alleviating secondary damage, and aids in the spinal cord's functional recovery [136]. The effectiveness of STS as a treatment in the early phases of spinal cord injury was first demonstrated by this study. Furthermore, Le Qi *et al.* established a rat model of SCI and discovered that Rb1 and Rh2 reduce the expression of inflammatory mediators to produce anti-inflammatory actions through toll-like receptor 4 (TLR4) and NF-κB pathways. When Xin-Wu Li *et al.* administered genistein to SCI mice, they discovered that the mice's Basso-Beattie-Bresnahan (BBB) scores were noticeably higher than those of the control group. They proposed that its anti-inflammatory mechanism may be associated with promoting M2 macrophage activation via inhibition of TLR4/MyD88/TRAF6 signaling [140].

5.3. Traditional Chinese Medicine

Ping Yang *et al.* discovered that the combination of bone marrow mesenchymal stem cell transplantation and Buyang Huanwu Decoction (BYHWD) considerably enhanced forelimb motor function in mice after SCI, exhibiting a synergistic effect on the neuroprotection of red nucleus neurons impacted by SCI, in contrast to individual treatments with BYHWD or bone marrow mesenchymal stem cell transplantation. The underlying mechanism may involve the upregulation of cAMP levels, activation of CREB, and subsequent phosphorylation of RhoA, which inhibits its downstream signaling pathways while promoting NGF expression [141]. Ding *et al.* used acupuncture in combination with bone marrow mesenchymal stem cell transplantation for treating SCI rats; after 10 weeks, they observed Rats undergoing spinal cord transection showed improved motor evoked potentials and higher Basso-Beattie-Bresnahan (BBB) scores [142]. Liu *et al.* reported that this combined treatment increased the survival rate of mesenchymal stem cells (MSCs). According to the suggested mechanism, acupuncture increases cAMP levels in the damaged spinal cord, which raises endogenous NT-3 expression and eventually promotes MSC differentiation into oligodendrocytes and neuron-like cells [143].

6. Summary and Discussion

As we continue to learn more about the mechanisms behind SCI, various rehabilitation physical therapy techniques, such as ultrasound stimulation, magnetic stimulation, and electrical stimulation, have made significant advancements [119] [144] [145]. For example, Ye-Hui Liao *et al.* demonstrated that low-intensity focused ultrasound applied to the lumbar vertebrae of SCI rats can stimulate neuronal cell membranes, thereby upregulating KCC2 expression, successfully activating spinal cord neural circuits and effectively alleviating spasticity in these animals [146]. A growing amount of studies have demonstrated the significance of traditional Chinese medicine in treating SCI models. In particular, it has been demonstrated that sodium tanshinone IIA sulfonate (STS) can lessen secondary injury, encourage spinal cord function recovery, and decrease the permeability of the injured blood-spinal cord barrier (BSCB) [136]. Triptolide exerts its effects by inhibiting certain inflammatory mediators through upregulation of miR-96 expression, ultimately facilitating spinal cord recovery. One hundred spinal cord damage patients participated in a randomized controlled trial, which found that acupuncture treatment administered during the early stages of post-injury significantly improved Functional Independence Measure scores [139]. Furthermore, acupuncture therapy has been shown to increase mesenchymal stem cells' capacity for differentiation in multiple investigations [142]. Despite the availability of numerous advanced treatment regimens, the intricacy of the neurological system and the permanent nature of nerve injury continue to pose significant challenges that hinder the rehabilitation process for patients with SCI. In 2001, Orlic *et al.* demonstrated through bone marrow stem cell transplantation that it could reconstitute cardiomyocytes and reduce infarct size. Although the encoding factors for stem cells involved in this pathway have not been confirmed in adult cardiomyocytes, this study established a theoretical foundation for subsequent developments in stem cell therapy and provided new hope for many clinically challenging diseases. In the treatment of spinal cord injuries, stem cell therapy has demonstrated significant promise [78]. Unlike conventional rehabilitation regimens, stem cells possess self-renewal capabilities and can differentiate into various cell types. Stem cell transplantation may exert its effects by reducing neuroinflammation and promoting axonal growth, among other mechanisms [125]. As currently the only potentially curative approach for SCI, stem cell therapy has garnered significant interest from numerous clinical research centers. Nowadays, mesenchymal stem cells, induced pluripotent stem cells, embryonic stem cells, and neural stem cells are among the many cell types used in stem cell treatment. Preliminary data suggests that stem cell transplantation is safe and feasible as scientists continue to progress their understanding of the pathophysiological mechanisms underlying SCI. MSCs have emerged as a compelling candidate in stem cell therapy due to their diverse sources, ease of isolation and accessibility, and exemption from ethical constraints. MSCs facilitate the recovery of both motor and sensory capabilities without causing major side effects by promoting cellular regeneration and

exerting immunomodulatory effects through the paracrine release of neurotrophic factors and inflammatory mediators. In a clinical study examining the effectiveness of UC-MSC therapy for SCI, intraventricular injection of UC-MSC was administered to 22 SCI patients, resulting in functional improvement in some individuals. Importantly, no significant adverse reactions were reported among all participants [120]. Earlier clinical trials and animal research have demonstrated the viability and safety of using different kinds of stem cells to treat SCI; however, despite the significant potential of stem cell therapy, the instability of the local microenvironment following SCI and the complexity of neural damage often result in several limitations when using stem cell therapy alone, including high costs and low survival rates [147]. Therefore, challenges such as low survival rates at the injury site necessitate further investigation into optimal administration routes and delivery vehicles. For example, Liang Wang *et al.* utilized a patch composed of micro-platelet-like graphene nanoplatelets combined with NSCs implanted into the subarachnoid space of SCI mice, which demonstrated improved hind limb activity. Notably, this electromagnetic cellular patch facilitated neuronal differentiation, increasing the proportion of neurons from 12.5% to 33.7%, thereby indicating its potential to enhance therapeutic efficacy in SCI treatment [119]. Min Chen *et al.* administered the treatment to rats with spinal cord injury by means of the combination of Bilobalide (a component isolated from ginkgo leaves) and BMSC transplantation. They found that, in contrast to any single therapy, the combined treatment of Bilobalide and BMSCs was more beneficial for the recovery of SCI. The study also unveiled that the mechanism of Bilobalide lies in promoting neuronal differentiation through the FMRP/WNK1 pathway [148]. The functionalized scaffolds have garnered significant attention for their potential to enhance the therapeutic efficacy of exosomes derived from mesenchymal stem cells. Research has demonstrated that the establishment of GS scaffolds enables the effective loading of these exosomes onto the scaffolds, facilitating their targeted delivery to injury sites and thereby synergistically promoting SCI repair [77]. These research outcomes manifest that in the future treatment of spinal cord injury, in contrast to single therapeutic modalities, the combination of multiple approaches will exhibit greater superiority and development potentiality. Recently emerging cell and bioengineering technologies may be considered for combined transplantation with stem cells to enhance their survival rate in the damaged area [149]. Biomaterials are substances that are compatible with tissues and have few harmful reactions when implanted. Its advantages lie in its exceptional biocompatibility and elimination of toxicity. Although biomaterials have been evaluated through in vitro and in vivo studies, further studies in higher-level animal models are needed to assess their clinical potential and safety concerns [149]. The incorporation of these novel technologies has the capacity to increase stem cell therapy's effectiveness for SCI, improve safety and immune compatibility, maximize the integration, survival, and transport of stem cells into host tissues, which will ultimately result in better clinical outcomes and more potent treatments [150].

For instance, advancements in reprogramming techniques could possibly address the moral issues around ESCs or iPSCs, thereby enhancing their therapeutic value for spinal cord injury. Recent developments in traditional Chinese medicine have revealed its significant therapeutic potential in SCI. Several animal studies that combine stem cell transplantation and traditional Chinese medicine have shown enhanced MSC survival rates, changes in the local microenvironment at the injury site, and enhanced targeted migration and differentiation of MSCs towards the spinal cord [141]. However, current research remains predominantly limited to animal models, and cell therapy protocols effective in rodents and primates may not translate effectively to human applications [151] [152]. As a basis for iterative practice and demonstration aimed at attaining clinical translation, future research will require a significant number of comparable case models and treatment approaches. Given that recovery from SCI is a prolonged process, psychological assessment along with timely and effective psychological interventions for patients is essential.

Conflicts of Interest

All authors declare that there has not been any commercial or associative interest that represents competing interests in connection with the work submitted.

References

[1] Shu, J., Cheng, F., Gong, Z., Ying, L., Wang, C., Yu, C., *et al.* (2020) Transplantation Strategies for Spinal Cord Injury Based on Microenvironment Modulation. *Current Stem Cell Research & Therapy*, **15**, 522-530. https://doi.org/10.2174/1574888x15666200421112622

[2] Alizadeh, A., Dyck, S.M. and Karimi-Abdolrezaee, S. (2019) Traumatic Spinal Cord Injury: An Overview of Pathophysiology, Models and Acute Injury Mechanisms. *Frontiers in Neurology*, **10**, Article No. 282. https://doi.org/10.3389/fneur.2019.00282

[3] Anjum, A., Yazid, M.D., Fauzi Daud, M., Idris, J., Ng, A.M.H., Selvi Naicker, A., *et al.* (2020) Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms. *International Journal of Molecular Sciences*, **21**, Article No. 7533. https://doi.org/10.3390/ijms21207533

[4] Khorasanizadeh, M., Yousefifard, M., Eskian, M., Lu, Y., Chalangari, M., Harrop, J.S., *et al.* (2019) Neurological Recovery Following Traumatic Spinal Cord Injury: A Systematic Review and Meta-Analysis. *Journal of Neurosurgery*: *Spine*, **30**, 683-699. https://doi.org/10.3171/2018.10.spine18802

[5] Nakhjavan-Shahraki, B., Yousefifard, M., Rahimi-Movaghar, V., Baikpour, M., Nasirinezhad, F., Safari, S., *et al.* (2018) Transplantation of Olfactory Ensheathing Cells on Functional Recovery and Neuropathic Pain after Spinal Cord Injury; Systematic Review and Meta-Analysis. *Scientific Reports*, **8**, Article No. 325. https://doi.org/10.1038/s41598-017-18754-4

[6] Martin-Lopez, M., Fernandez-Muñoz, B. and Canovas, S. (2021) Pluripotent Stem Cells for Spinal Cord Injury Repair. *Cells*, **10**, Article No. 3334. https://doi.org/10.3390/cells10123334

[7] Wilson, J.R., Tetreault, L.A., Kwon, B.K., Arnold, P.M., Mroz, T.E., Shaffrey, C., *et al.*

(2017) Timing of Decompression in Patients with Acute Spinal Cord Injury: A Systematic Review. *Global Spine Journal*, **7**, 95S-115S. https://doi.org/10.1177/2192568217701716

[8] Liu, Z., Yang, Y., He, L., Pang, M., Luo, C., Liu, B., *et al.* (2019) High-Dose Methylprednisolone for Acute Traumatic Spinal Cord Injury. *Neurology*, **93**, e841-e850. https://doi.org/10.1212/wnl.0000000000007998

[9] Sheerin, F. (2004) Spinal Cord Injury: Anatomy and Physiology of the Spinal Cord. *Emergency Nurse*, **12**, 30-36. https://doi.org/10.7748/en2004.12.12.8.30.c1178

[10] O'Shea, T.M., Burda, J.E. and Sofroniew, M.V. (2017) Cell Biology of Spinal Cord Injury and Repair. *Journal of Clinical Investigation*, **127**, 3259-3270. https://doi.org/10.1172/jci90608

[11] Guest, J., Datta, N., Jimsheleishvili, G. and Gater, D.R. (2022) Pathophysiology, Classification and Comorbidities after Traumatic Spinal Cord Injury. *Journal of Personalized Medicine*, **12**, Article No. 1126. https://doi.org/10.3390/jpm12071126

[12] El Masri, J., Fadlallah, H., Al Sabsabi, R., Afyouni, A., Al-Sayegh, M. and Abou-Kheir, W. (2024) Adipose-Derived Stem Cell Therapy in Spinal Cord Injury. *Cells*, **13**, Article No. 1505. https://doi.org/10.3390/cells13171505

[13] Oyinbo, C. (2011) Secondary Injury Mechanisms in Traumatic Spinal Cord Injury: A Nugget of This Multiply Cascade. *Acta Neurobiologiae Experimentalis*, **71**, 281-299. https://doi.org/10.55782/ane-2011-1848

[14] Eli, I., Lerner, D.P. and Ghogawala, Z. (2021) Acute Traumatic Spinal Cord Injury. *Neurologic Clinics*, **39**, 471-488. https://doi.org/10.1016/j.ncl.2021.02.004

[15] Gordh, T., Chu, H. and Sharma, H.S. (2006) Spinal Nerve Lesion Alters Blood-Spinal Cord Barrier Function and Activates Astrocytes in the Rat. *Pain*, **124**, 211-221. https://doi.org/10.1016/j.pain.2006.05.020

[16] Deng, L., Lv, J.Q. and Sun, L. (2022) Experimental Treatments to Attenuate Blood Spinal Cord Barrier Rupture in Rats with Traumatic Spinal Cord Injury: A Meta-Analysis and Systematic Review. *Frontiers in Pharmacology*, **13**, Article ID: 950368. https://doi.org/10.3389/fphar.2022.950368

[17] Fan, B., Wei, Z., Yao, X., Shi, G., Cheng, X., Zhou, X., *et al.* (2018) Microenvironment Imbalance of Spinal Cord Injury. *Cell Transplantation*, **27**, 853-866. https://doi.org/10.1177/0963689718755778

[18] Hawryluk, G., Whetstone, W., Saigal, R., Ferguson, A., Talbott, J., Bresnahan, J., *et al.* (2015) Mean Arterial Blood Pressure Correlates with Neurological Recovery after Human Spinal Cord Injury: Analysis of High Frequency Physiologic Data. *Journal of Neurotrauma*, **32**, 1958-1967. https://doi.org/10.1089/neu.2014.3778

[19] Karimi-Abdolrezaee, S., Eftekharpour, E. and Fehlings, M.G. (2004) Temporal and Spatial Patterns of Kv1.1 and Kv1.2 Protein and Gene Expression in Spinal Cord White Matter after Acute and Chronic Spinal Cord Injury in Rats: Implications for Axonal Pathophysiology after Neurotrauma. *European Journal of Neuroscience*, **19**, 577-589. https://doi.org/10.1111/j.0953-816x.2004.03164.x

[20] Khan, S.I., Ahmed, N., Ahsan, K., Abbasi, M., Maugeri, R., Chowdhury, D., *et al.* (2023) An Insight into the Prospects and Drawbacks of Stem Cell Therapy for Spinal Cord Injuries: Ongoing Trials and Future Directions. *Brain Sciences*, **13**, Article No. 1697. https://doi.org/10.3390/brainsci13121697

[21] Tator, C.H. and Koyanagi, I. (1997) Vascular Mechanisms in the Pathophysiology of Human Spinal Cord Injury. *Journal of Neurosurgery*, **86**, 483-492. https://doi.org/10.3171/jns.1997.86.3.0483

[22] Vanzulli, I. and Butt, A.M. (2015) Mglur5 Protect Astrocytes from Ischemic Damage in Postnatal CNS White Matter. *Cell Calcium*, **58**, 423-430. https://doi.org/10.1016/j.ceca.2015.06.010

[23] Jha, R.M., Kochanek, P.M. and Simard, J.M. (2019) Pathophysiology and Treatment of Cerebral Edema in Traumatic Brain Injury. *Neuropharmacology*, **145**, 230-246. https://doi.org/10.1016/j.neuropharm.2018.08.004

[24] Sharma, H.S. (2010) Early Microvascular Reactions and Blood-spinal Cord Barrier Disruption Are Instrumental in Pathophysiology of Spinal Cord Injury and Repair: Novel Therapeutic Strategies Including Nanowired Drug Delivery to Enhance Neuroprotection. *Journal of Neural Transmission*, **118**, 155-176. https://doi.org/10.1007/s00702-010-0514-4

[25] Zhou, H., Wang, L., Xu, Q., Fan, Z., Zhu, Y., Jiang, H., *et al.* (2016) Downregulation of miR-199b Promotes the Acute Spinal Cord Injury through IKKβ-NF-κB Signaling Pathway Activating Microglial Cells. *Experimental Cell Research*, **349**, 60-67. https://doi.org/10.1016/j.yexcr.2016.09.020

[26] Fu, H., Zhao, Y., Hu, D., Wang, S., Yu, T. and Zhang, L. (2020) Depletion of Microglia Exacerbates Injury and Impairs Function Recovery after Spinal Cord Injury in Mice. *Cell Death & Disease*, **11**, Article No. 528. https://doi.org/10.1038/s41419-020-2733-4

[27] Kjell, J. and Olson, L. (2016) Rat Models of Spinal Cord Injury: From Pathology to Potential Therapies. *Disease Models & Mechanisms*, **9**, 1125-1137. https://doi.org/10.1242/dmm.025833

[28] Kettenmann, H., Hanisch, U., Noda, M. and Verkhratsky, A. (2011) Physiology of Microglia. *Physiological Reviews*, **91**, 461-553. https://doi.org/10.1152/physrev.00011.2010

[29] Salter, M.W. and Stevens, B. (2017) Microglia Emerge as Central Players in Brain Disease. *Nature Medicine*, **23**, 1018-1027. https://doi.org/10.1038/nm.4397

[30] Colton, C.A. (2009) Heterogeneity of Microglial Activation in the Innate Immune Response in the Brain. *Journal of Neuroimmune Pharmacology*, **4**, 399-418. https://doi.org/10.1007/s11481-009-9164-4

[31] Orihuela, R., McPherson, C.A. and Harry, G.J. (2015) Microglial M1/M2 Polarization and Metabolic States. *British Journal of Pharmacology*, **173**, 649-665. https://doi.org/10.1111/bph.13139

[32] Kobashi, S., Terashima, T., Katagi, M., Nakae, Y., Okano, J., Suzuki, Y., *et al.* (2020) Transplantation of M2-Deviated Microglia Promotes Recovery of Motor Function after Spinal Cord Injury in Mice. *Molecular Therapy*, **28**, 254-265. https://doi.org/10.1016/j.ymthe.2019.09.004

[33] Dong, L., Dongzhi, Z., Jin, Y., Kim, Y., Lee, D., Huang, S., *et al.* (2020) *Taraxacum officinale* Wigg. Attenuates Inflammatory Responses in Murine Microglia through the Nrf2/HO-1 and NF-κB Signaling Pathways. *The American Journal of Chinese Medicine*, **48**, 445-462. https://doi.org/10.1142/s0192415x20500238

[34] Balla, G., Jacob, H.S., Balla, J., Rosenberg, M., Nath, K., Apple, F., *et al.* (1992) Ferritin: A Cytoprotective Antioxidant Strategem of Endothelium. *Journal of Biological Chemistry*, **267**, 18148-18153. https://doi.org/10.1016/s0021-9258(19)37165-0

[35] Sofroniew, M.V. and Vinters, H.V. (2009) Astrocytes: Biology and Pathology. *Acta Neuropathologica*, **119**, 7-35. https://doi.org/10.1007/s00401-009-0619-8

[36] Cregg, J.M., DePaul, M.A., Filous, A.R., Lang, B.T., Tran, A. and Silver, J. (2014) Functional Regeneration beyond the Glial Scar. *Experimental Neurology*, **253**, 197-207. https://doi.org/10.1016/j.expneurol.2013.12.024

[37] Kamakura, S., Oishi, K., Yoshimatsu, T., Nakafuku, M., Masuyama, N. and Gotoh, Y. (2004) Hes Binding to STAT3 Mediates Crosstalk between Notch and JAK-STAT Signalling. *Nature Cell Biology*, **6**, 547-554. https://doi.org/10.1038/ncb1138

[38] Liddelow, S.A. and Barres, B.A. (2017) Reactive Astrocytes: Production, Function, and Therapeutic Potential. *Immunity*, **46**, 957-967. https://doi.org/10.1016/j.immuni.2017.06.006

[39] Diniz, L.P., Matias, I.C.P., Garcia, M.N. and Gomes, F.C.A. (2014) Astrocytic Control of Neural Circuit Formation: Highlights on Tgf-Beta Signaling. *Neurochemistry International*, **78**, 18-27. https://doi.org/10.1016/j.neuint.2014.07.008

[40] Sabelström, H., Stenudd, M., Réu, P., Dias, D.O., Elfineh, M., Zdunek, S., *et al.* (2013) Resident Neural Stem Cells Restrict Tissue Damage and Neuronal Loss after Spinal Cord Injury in Mice. *Science*, **342**, 637-640. https://doi.org/10.1126/science.1242576

[41] Pekny, M. and Nilsson, M. (2005) Astrocyte Activation and Reactive Gliosis. *Glia*, **50**, 427-434. https://doi.org/10.1002/glia.20207

[42] Xie, C., Shen, X., Xu, X., Liu, H., Li, F., Lu, S., *et al.* (2020) Astrocytic YAP Promotes the Formation of Glia Scars and Neural Regeneration after Spinal Cord Injury. *The Journal of Neuroscience*, **40**, 2644-2662. https://doi.org/10.1523/jneurosci.2229-19.2020

[43] Alessi, D.R., James, S.R., Downes, C.P., Holmes, A.B., Gaffney, P.R.J., Reese, C.B., *et al.* (1997) Characterization of a 3-Phosphoinositide-Dependent Protein Kinase Which Phosphorylates and Activates Protein Kinase Bα. *Current Biology*, **7**, 261-269. https://doi.org/10.1016/s0960-9822(06)00122-9

[44] Sarbassov, D.D., Guertin, D.A., Ali, S.M. and Sabatini, D.M. (2005) Phosphorylation and Regulation of Akt/PKB by the Rictor-mTOR Complex. *Science*, **307**, 1098-1101. https://doi.org/10.1126/science.1106148

[45] Hara, M., Kobayakawa, K., Ohkawa, Y., Kumamaru, H., Yokota, K., Saito, T., *et al.* (2017) Interaction of Reactive Astrocytes with Type I Collagen Induces Astrocytic Scar Formation through the Integrin-n-Cadherin Pathway after Spinal Cord Injury. *Nature Medicine*, **23**, 818-828. https://doi.org/10.1038/nm.4354

[46] Yan, L., Li, Z., Li, C., Chen, J., Zhou, X., Cui, J., *et al.* (2024) Hspb1 and Lgals3 in Spinal Neurons Are Closely Associated with Autophagy Following Excitotoxicity Based on Machine Learning Algorithms. *PLOS ONE*, **19**, e0303235. https://doi.org/10.1371/journal.pone.0303235

[47] Taoka, Y., Okajima, K., Uchiba, M., Murakami, K., Kushimoto, S., Johno, M., *et al.* (1997) Role of Neutrophils in Spinal Cord Injury in the Rat. *Neuroscience*, **79**, 1177-1182. https://doi.org/10.1016/s0306-4522(97)00011-0

[48] Bao, F., Chen, Y., Dekaban, G.A. and Weaver, L.C. (2004) Early Anti-Inflammatory Treatment Reduces Lipid Peroxidation and Protein Nitration after Spinal Cord Injury in Rats. *Journal of Neurochemistry*, **88**, 1335-1344. https://doi.org/10.1046/j.1471-4159.2003.02240.x

[49] Bains, M. and Hall, E.D. (2012) Antioxidant Therapies in Traumatic Brain and Spinal Cord Injury. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1822**, 675-684. https://doi.org/10.1016/j.bbadis.2011.10.017

[50] Feng, Z., Min, L., Liang, L., Chen, B., Chen, H., Zhou, Y., *et al.* (2021) Neutrophil Extracellular Traps Exacerbate Secondary Injury via Promoting Neuroinflammation and Blood-Spinal Cord Barrier Disruption in Spinal Cord Injury. *Frontiers in Immunology*, **12**, Article ID: 698249. https://doi.org/10.3389/fimmu.2021.698249

[51] Brinkmann, V., Reichard, U., Goosmann, C., Fauler, B., Uhlemann, Y., Weiss, D.S.,

et al. (2004) Neutrophil Extracellular Traps Kill Bacteria. *Science*, **303**, 1532-1535. https://doi.org/10.1126/science.1092385

[52] Kurimoto, T., Yin, Y., Habboub, G., Gilbert, H., Li, Y., Nakao, S., *et al.* (2013) Neutrophils Express Oncomodulin and Promote Optic Nerve Regeneration. *The Journal of Neuroscience*, **33**, 14816-14824. https://doi.org/10.1523/jneurosci.5511-12.2013

[53] Sas, A.R., Carbajal, K.S., Jerome, A.D., Menon, R., Yoon, C., Kalinski, A.L., *et al.* (2020) A New Neutrophil Subset Promotes CNS Neuron Survival and Axon Regeneration. *Nature Immunology*, **21**, 1496-1505. https://doi.org/10.1038/s41590-020-00813-0

[54] Stirling, D.P., Liu, S., Kubes, P. and Yong, V.W. (2009) Depletion of Ly6g/Gr-1 Leukocytes after Spinal Cord Injury in Mice Alters Wound Healing and Worsens Neurological Outcome. *The Journal of Neuroscience*, **29**, 753-764. https://doi.org/10.1523/jneurosci.4918-08.2009

[55] Silva, M.T. (2009) When Two Is Better than One: Macrophages and Neutrophils Work in Concert in Innate Immunity as Complementary and Cooperative Partners of a Myeloid Phagocyte System. *Journal of Leukocyte Biology*, **87**, 93-106. https://doi.org/10.1189/jlb.0809549

[56] Wang, X., Cao, K., Sun, X., Chen, Y., Duan, Z., Sun, L., *et al.* (2014) Macrophages in Spinal Cord Injury: Phenotypic and Functional Change from Exposure to Myelin Debris. *Glia*, **63**, 635-651. https://doi.org/10.1002/glia.22774

[57] Kigerl, K.A., Gensel, J.C., Ankeny, D.P., Alexander, J.K., Donnelly, D.J. and Popovich, P.G. (2009) Identification of Two Distinct Macrophage Subsets with Divergent Effects Causing Either Neurotoxicity or Regeneration in the Injured Mouse Spinal Cord. *The Journal of Neuroscience*, **29**, 13435-13444. https://doi.org/10.1523/jneurosci.3257-09.2009

[58] Kroner, A., Greenhalgh, A.D., Zarruk, J.G., Passos dos Santos, R., Gaestel, M. and David, S. (2014) TNF and Increased Intracellular Iron Alter Macrophage Polarization to a Detrimental M1 Phenotype in the Injured Spinal Cord. *Neuron*, **83**, 1098-1116. https://doi.org/10.1016/j.neuron.2014.07.027

[59] Madalena, K.M., Brennan, F.H. and Popovich, P.G. (2022) Genetic Deletion of the Glucocorticoid Receptor in Cx3Cr1+ Myeloid Cells Is Neuroprotective and Improves Motor Recovery after Spinal Cord Injury. *Experimental Neurology*, **355**, Article ID: 114114. https://doi.org/10.1016/j.expneurol.2022.114114

[60] Zhu, Y., Lyapichev, K., Lee, D.H., Motti, D., Ferraro, N.M., Zhang, Y., *et al.* (2017) Macrophage Transcriptional Profile Identifies Lipid Catabolic Pathways That Can Be Therapeutically Targeted after Spinal Cord Injury. *The Journal of Neuroscience*, **37**, 2362-2376. https://doi.org/10.1523/jneurosci.2751-16.2017

[61] Hall, E.D. (1989) Pathophysiology of Spinal Cord Injury. Current and Future Therapies. *Minerva Anestesiologica*, **55**, 63-66.

[62] Dumont, R.J., Okonkwo, D.O., Verma, S., Hurlbert, R.J., Boulos, P.T., Ellegala, D.B., *et al.* (2001) Acute Spinal Cord Injury, Part I: Pathophysiologic Mechanisms. *Clinical Neuropharmacology*, **24**, 254-264. https://doi.org/10.1097/00002826-200109000-00002

[63] Tran, A.P., Warren, P.M. and Silver, J. (2018) The Biology of Regeneration Failure and Success after Spinal Cord Injury. *Physiological Reviews*, **98**, 881-917. https://doi.org/10.1152/physrev.00017.2017

[64] Quinones, C., Wilson, J.P., Kumbhare, D., Guthikonda, B. and Hoang, S. (2024) Clinical Assessment and Management of Acute Spinal Cord Injury. *Journal of Clinical Medicine*, **13**, Article No. 5719. https://doi.org/10.3390/jcm13195719

[65] Hurlbert, R.J., Hadley, M.N., Walters, B.C., Aarabi, B., Dhall, S.S., Gelb, D.E., *et al.* (2015) Pharmacological Therapy for Acute Spinal Cord Injury. *Neurosurgery*, **76**, S71-S83. https://doi.org/10.1227/01.neu.0000462080.04196.f7

[66] Suberviola, B., González-Castro, A., Llorca, J., Ortiz-Melón, F. and Miñambres, E. (2008) Early Complications of High-Dose Methylprednisolone in Acute Spinal Cord Injury Patients. *Injury*, **39**, 748-752. https://doi.org/10.1016/j.injury.2007.12.005

[67] Lambrechts, M.J. and Cook, J.L. (2020) Nonsteroidal Anti-Inflammatory Drugs and Their Neuroprotective Role after an Acute Spinal Cord Injury: A Systematic Review of Animal Models. *Global Spine Journal*, **11**, 365-377. https://doi.org/10.1177/2192568220901689

[68] Sterner, R.C. and Sterner, R.M. (2023) Immune Response Following Traumatic Spinal Cord Injury: Pathophysiology and Therapies. *Frontiers in Immunology*, **13**, Article ID: 1084101. https://doi.org/10.3389/fimmu.2022.1084101

[69] Casha, S., Zygun, D., McGowan, M.D., Bains, I., Yong, V.W. and John Hurlbert, R. (2012) Results of a Phase II Placebo-Controlled Randomized Trial of Minocycline in Acute Spinal Cord Injury. *Brain*, **135**, 1224-1236. https://doi.org/10.1093/brain/aws072

[70] Geisler, F.H., Dorsey, F.C. and Coleman, W.P. (1991) Recovery of Motor Function after Spinal-Cord Injury—A Randomized, Placebo-Controlled Trial with GM-1 Ganglioside. *New England Journal of Medicine*, **324**, 1829-1838. https://doi.org/10.1056/nejm199106273242601

[71] Fehlings, M.G., Vaccaro, A., Wilson, J.R., Singh, A., W. Cadotte, D., Harrop, J.S., *et al.* (2012) Early versus Delayed Decompression for Traumatic Cervical Spinal Cord Injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PLOS ONE*, **7**, e32037. https://doi.org/10.1371/journal.pone.0032037

[72] Dimar, J.R., Glassman, S.D., Raque, G.H., Zhang, Y.P. and Shields, C.B. (1999) The Influence of Spinal Canal Narrowing and Timing of Decompression on Neurologic Recovery after Spinal Cord Contusion in a Rat Model. *Spine*, **24**, Article No. 1623. https://doi.org/10.1097/00007632-199908150-00002

[73] Fehlings, M.G., Sekhon, L.H.S. and Tator, C. (2001) The Role and Timing of Decompression in Acute Spinal Cord Injury: What Do We Know? What Should We Do? *Spine*, **26**, S101-S110. https://doi.org/10.1097/00007632-200112151-00017

[74] Jug, M., Komadina, R., Wendt, K., Pape, H.C., Bloemers, F. and Nau, C. (2024) Thoracolumbar Spinal Cord Injury: Management, Techniques, Timing. *European Journal of Trauma and Emergency Surgery*, **50**, 1969-1975. https://doi.org/10.1007/s00068-024-02595-8

[75] Glinsky, J.V. and Harvey, L.A. (2024) Physiotherapy Management of People with Spinal Cord Injuries: An Update. *Journal of Physiotherapy*, **70**, 256-264. https://doi.org/10.1016/j.jphys.2024.09.008

[76] Sunshine, M.D., Bindi, V.E., Nguyen, B.L., Doerr, V., Boeno, F.P., Chandran, V., *et al.* (2023) Oxygen Therapy Attenuates Neuroinflammation after Spinal Cord Injury. *Journal of Neuroinflammation*, **20**, Article No. 303. https://doi.org/10.1186/s12974-023-02985-6

[77] Huang, T., Mu, J., Wu, J., Cao, J., Zhang, X., Guo, J., *et al.* (2024) A Functionalized Scaffold Facilitates Neurites Extension for Spinal Cord Injury Therapy. *Small*, **20**, e2401020. https://doi.org/10.1002/smll.202401020

[78] Orlic, D., Kajstura, J., Chimenti, S., Jakoniuk, I., Anderson, S.M., Li, B., *et al.* (2001) Bone Marrow Cells Regenerate Infarcted Myocardium. *Nature*, **410**, 701-705. https://doi.org/10.1038/35070587

[79] Araujo, T.P.F., Cristante, A.F., Marcon, R.M., Santos, G.B.d., Nicola, M.H.A., Araujo, A.O.d., *et al.* (2024) Improvement of Motor Function in Mice after Implantation of Mononuclear Stem Cells from Human Umbilical Cord and Placenta Blood after 3 and 6 Weeks of Experimental Spinal Cord Injury. *Clinics*, **79**, Article ID: 100509. https://doi.org/10.1016/j.clinsp.2024.100509

[80] Macêdo, C.T., de Freitas Souza, B.S., Villarreal, C.F., Silva, D.N., da Silva, K.N., de Souza, C.L.e.M., *et al.* (2024) Transplantation of Autologous Mesenchymal Stromal Cells in Complete Cervical Spinal Cord Injury: A Pilot Study. *Frontiers in Medicine*, **11**, Article ID: 1451297. https://doi.org/10.3389/fmed.2024.1451297

[81] Deokate, N., Acharya, S., Patil, R., Shaikh, S.M. and Karwa, V. (2024) A Comprehensive Review of the Role of Stem Cells in Neuroregeneration: Potential Therapies for Neurological Disorders. *Cureus*, **16**, e67506. https://doi.org/10.7759/cureus.67506

[82] Mili, B. and Choudhary, O.P. (2024) Advancements and Mechanisms of Stem Cell-Based Therapies for Spinal Cord Injury in Animals. *International Journal of Surgery*, **110**, 6182-6197. https://doi.org/10.1097/js9.0000000000001074

[83] Zaripova, L.N., Midgley, A., Christmas, S.E., Beresford, M.W., Pain, C., Baildam, E.M., *et al.* (2023) Mesenchymal Stem Cells in the Pathogenesis and Therapy of Autoimmune and Autoinflammatory Diseases. *International Journal of Molecular Sciences*, **24**, Article No. 16040. https://doi.org/10.3390/ijms242216040

[84] Evans, M.J. and Kaufman, M.H. (1981) Establishment in Culture of Pluripotential Cells from Mouse Embryos. *Nature*, **292**, 154-156. https://doi.org/10.1038/292154a0

[85] Hussen, B.M., Taheri, M., Yashooa, R.K., Abdullah, G.H., Abdullah, S.R., Kheder, R.K., *et al.* (2024) Revolutionizing Medicine: Recent Developments and Future Prospects in Stem-Cell Therapy. *International Journal of Surgery*, **110**, 8002-8024. https://doi.org/10.1097/js9.0000000000002109

[86] Zeng, C. (2023) Advancing Spinal Cord Injury Treatment through Stem Cell Therapy: A Comprehensive Review of Cell Types, Challenges, and Emerging Technologies in Regenerative Medicine. *International Journal of Molecular Sciences*, **24**, Article No. 14349. https://doi.org/10.3390/ijms241814349

[87] Singh, V.K., Kumar, N., Kalsan, M., Saini, A. and Chandra, R. (2015) Mechanism of Induction: Induced Pluripotent Stem Cells (iPSCs). *Journal of Stem Cells*, **10**, 43-62.

[88] Nori, S., Okada, Y., Yasuda, A., Tsuji, O., Takahashi, Y., Kobayashi, Y., *et al.* (2011) Grafted Human-Induced Pluripotent Stem-Cell-Derived Neurospheres Promote Motor Functional Recovery after Spinal Cord Injury in Mice. *Proceedings of the National Academy of Sciences*, **108**, 16825-16830. https://doi.org/10.1073/pnas.1108077108

[89] Kobayashi, Y., Okada, Y., Itakura, G., Iwai, H., Nishimura, S., Yasuda, A., *et al.* (2012) Pre-Evaluated Safe Human IPSC-Derived Neural Stem Cells Promote Functional Recovery after Spinal Cord Injury in Common Marmoset without Tumorigenicity. *PLOS ONE*, **7**, e52787. https://doi.org/10.1371/journal.pone.0052787

[90] Gong, Z., Xia, K., Xu, A., Yu, C., Wang, C., Zhu, J., *et al.* (2020) Stem Cell Transplantation: A Promising Therapy for Spinal Cord Injury. *Current Stem Cell Research & Therapy*, **15**, 321-331. https://doi.org/10.2174/1574888x14666190823144424

[91] Morshead, C.M., Reynolds, B.A., Craig, C.G., McBurney, M.W., Staines, W.A., Morassutti, D., *et al.* (1994) Neural Stem Cells in the Adult Mammalian Forebrain: A Relatively Quiescent Subpopulation of Subependymal Cells. *Neuron*, **13**, 1071-1082. https://doi.org/10.1016/0896-6273(94)90046-9

[92] Gage, F.H. (2000) Mammalian Neural Stem Cells. *Science*, **287**, 1433-1438. https://doi.org/10.1126/science.287.5457.1433

[93] Butruille, L., Batailler, M., Cateau, M., Sharif, A., Leysen, V., Prévot, V., *et al.* (2022) Selective Depletion of Adult GFAP-Expressing Tanycytes Leads to Hypogonadotropic Hypogonadism in Males. *Frontiers in Endocrinology*, **13**, Article ID: 869019. https://doi.org/10.3389/fendo.2022.869019

[94] Emgård, M., Piao, J., Aineskog, H., Liu, J., Calzarossa, C., Odeberg, J., *et al.* (2014) Neuroprotective Effects of Human Spinal Cord-Derived Neural Precursor Cells after Transplantation to the Injured Spinal Cord. *Experimental Neurology*, **253**, 138-145. https://doi.org/10.1016/j.expneurol.2013.12.022

[95] Iwanami, A., Kaneko, S., Nakamura, M., Kanemura, Y., Mori, H., Kobayashi, S., *et al.* (2005) Transplantation of Human Neural Stem Cells for Spinal Cord Injury in Primates. *Journal of Neuroscience Research*, **80**, 182-190. https://doi.org/10.1002/jnr.20436

[96] Ma, Z., Liu, T., Liu, L., Pei, Y., Wang, T., Wang, Z., *et al.* (2024) Epidermal Neural Crest Stem Cell Conditioned Medium Enhances Spinal Cord Injury Recovery via PI3K/AKT-Mediated Neuronal Apoptosis Suppression. *Neurochemical Research*, **49**, 2854-2870. https://doi.org/10.1007/s11064-024-04207-8

[97] Karimi-Haghighi, S., Chavoshinezhad, S., Safari, A., Razeghian-Jahromi, I., jamhiri, I., Khodabandeh, Z., *et al.* (2022) Preconditioning with Secretome of Neural Crest-Derived Stem Cells Enhanced Neurotrophic Expression in Mesenchymal Stem Cells. *Neuroscience Letters*, **773**, Article ID: 136511. https://doi.org/10.1016/j.neulet.2022.136511

[98] Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F.C., Krause, D.S., *et al.* (2006) Minimal Criteria for Defining Multipotent Mesenchymal Stromal Cells. the International Society for Cellular Therapy Position Statement. *Cytotherapy*, **8**, 315-317. https://doi.org/10.1080/14653240600855905

[99] Yuan, X., Wu, Q., Wang, P., Jing, Y., Yao, H., Tang, Y., *et al.* (2019) Exosomes Derived from Pericytes Improve Microcirculation and Protect Blood-Spinal Cord Barrier after Spinal Cord Injury in Mice. *Frontiers in Neuroscience*, **13**, Article No. 319. https://doi.org/10.3389/fnins.2019.00319

[100] Cofano, F., Boido, M., Monticelli, M., Zenga, F., Ducati, A., Vercelli, A., *et al.* (2019) Mesenchymal Stem Cells for Spinal Cord Injury: Current Options, Limitations, and Future of Cell Therapy. *International Journal of Molecular Sciences*, **20**, Article No. 2698. https://doi.org/10.3390/ijms20112698

[101] Zhang, W., Zhang, F., Shi, H., Tan, R., Han, S., Ye, G., *et al.* (2014) Comparisons of Rabbit Bone Marrow Mesenchymal Stem Cell Isolation and Culture Methods *in Vitro*. *PLOS ONE*, **9**, e88794. https://doi.org/10.1371/journal.pone.0088794

[102] Moviglia, G.A., Varela, G., Brizuela, J.A., Moviglia Brandolino, M.T., Farina, P., Etchegaray, G., *et al.* (2009) Case Report on the Clinical Results of a Combined Cellular Therapy for Chronic Spinal Cord Injured Patients. *Spinal Cord*, **47**, 499-503. https://doi.org/10.1038/sc.2008.164

[103] Sorrell, J.M., Baber, M.A. and Caplan, A.I. (2009) Influence of Adult Mesenchymal Stem Cells On*in Vitro* Vascular Formation. *Tissue Engineering Part A*, **15**, 1751-1761. https://doi.org/10.1089/ten.tea.2008.0254

[104] Kadoya, K., Lu, P., Nguyen, K., Lee-Kubli, C., Kumamaru, H., Yao, L., *et al.* (2016) Spinal Cord Reconstitution with Homologous Neural Grafts Enables Robust Corticospinal Regeneration. *Nature Medicine*, **22**, 479-487. https://doi.org/10.1038/nm.4066

[105] Forostyak, S., Jendelova, P. and Sykova, E. (2013) The Role of Mesenchymal Stromal Cells in Spinal Cord Injury, Regenerative Medicine and Possible Clinical

Applications. *Biochimie*, **95**, 2257-2270. https://doi.org/10.1016/j.biochi.2013.08.004

[106] Uccelli, A., Benvenuto, F., Laroni, A. and Giunti, D. (2011) Neuroprotective Features of Mesenchymal Stem Cells. *Best Practice & Research Clinical Haematology*, **24**, 59-64. https://doi.org/10.1016/j.beha.2011.01.004

[107] Hwang, J., Jang, S., Kim, C., Lee, S. and Jeong, H. (2023) Role of Stem Cell-Derived Exosomes and MicroRNAs in Spinal Cord Injury. *International Journal of Molecular Sciences*, **24**, Article No. 13849. https://doi.org/10.3390/ijms241813849

[108] Lee, S.Y., Kwon, B., Lee, K., Son, Y.H. and Chung, S.G. (2017) Therapeutic Mechanisms of Human Adipose-Derived Mesenchymal Stem Cells in a Rat Tendon Injury Model. *The American Journal of Sports Medicine*, **45**, 1429-1439. https://doi.org/10.1177/0363546517689874

[109] Silva, N.A., Sousa, N., Reis, R.L. and Salgado, A.J. (2014) From Basics to Clinical: A Comprehensive Review on Spinal Cord Injury. *Progress in Neurobiology*, **114**, 25-57. https://doi.org/10.1016/j.pneurobio.2013.11.002

[110] Ahuja, C.S., Wilson, J.R., Nori, S., Kotter, M.R.N., Druschel, C., Curt, A., *et al.* (2017) Traumatic Spinal Cord Injury. *Nature Reviews Disease Primers*, **3**, Article No. 17018. https://doi.org/10.1038/nrdp.2017.18

[111] Lo Sicco, C., Reverberi, D., Balbi, C., Ulivi, V., Principi, E., Pascucci, L., *et al.* (2017) Mesenchymal Stem Cell-Derived Extracellular Vesicles as Mediators of Anti-Inflammatory Effects: Endorsement of Macrophage Polarization. *Stem Cells Translational Medicine*, **6**, 1018-1028. https://doi.org/10.1002/sctm.16-0363

[112] Michelo, C.M., Fasse, E., van Cranenbroek, B., Linda, K., van der Meer, A., Abdelrazik, H., *et al.* (2016) Added Effects of Dexamethasone and Mesenchymal Stem Cells on Early Natural Killer Cell Activation. *Transplant Immunology*, **37**, 1-9. https://doi.org/10.1016/j.trim.2016.04.008

[113] Lu, Y., Liu, J., Liu, Y., Qin, Y., Luo, Q., Wang, Q., *et al.* (2015) TLR4 Plays a Crucial Role in MSC-Induced Inhibition of NK Cell Function. *Biochemical and Biophysical Research Communications*, **464**, 541-547. https://doi.org/10.1016/j.bbrc.2015.07.002

[114] Zurita, M., Vaquero, J., Bonilla, C., Santos, M., De Haro, J., Oya, S., *et al.* (2008) Functional Recovery of Chronic Paraplegic Pigs after Autologous Transplantation of Bone Marrow Stromal Cells. *Transplantation*, **86**, 845-853. https://doi.org/10.1097/tp.0b013e318186198f

[115] Ide, C., Nakai, Y., Nakano, N., Seo, T., Yamada, Y., Endo, K., *et al.* (2010) Bone Marrow Stromal Cell Transplantation for Treatment of Sub-Acute Spinal Cord Injury in the Rat. *Brain Research*, **1332**, 32-47. https://doi.org/10.1016/j.brainres.2010.03.043

[116] Zhou, Z., Tian, X., Mo, B., Xu, H., Zhang, L., Huang, L., *et al.* (2020) Adipose Mesenchymal Stem Cell Transplantation Alleviates Spinal Cord Injury-Induced Neuroinflammation Partly by Suppressing the Jagged1/notch Pathway. *Stem Cell Research & Therapy*, **11**, Article No. 212. https://doi.org/10.1186/s13287-020-01724-5

[117] Hur, J.W., Cho, T., Park, D., Lee, J., Park, J. and Chung, Y. (2015) Intrathecal Transplantation of Autologous Adipose-Derived Mesenchymal Stem Cells for Treating Spinal Cord Injury: A Human Trial. *The Journal of Spinal Cord Medicine*, **39**, 655-664. https://doi.org/10.1179/2045772315y.0000000048

[118] Bydon, M., Qu, W., Moinuddin, F.M., Hunt, C.L., Garlanger, K.L., Reeves, R.K., *et al.* (2024) Intrathecal Delivery of Adipose-Derived Mesenchymal Stem Cells in Traumatic Spinal Cord Injury: Phase I Trial. *Nature Communications*, **15**, Article No. 2201. https://doi.org/10.1038/s41467-024-46259-y

[119] Wang, L., Zhao, H., Han, M., Yang, H., Lei, M., Wang, W., *et al.* (2024) Electromagnetic

Cellularized Patch with Wirelessly Electrical Stimulation for Promoting Neuronal Differentiation and Spinal Cord Injury Repair. *Advanced Science*, **11**, e2307527. https://doi.org/10.1002/advs.202307527

[120] Liu, J., Han, D., Wang, Z., Xue, M., Zhu, L., Yan, H., *et al.* (2013) Clinical Analysis of the Treatment of Spinal Cord Injury with Umbilical Cord Mesenchymal Stem Cells. *Cytotherapy*, **15**, 185-191. https://doi.org/10.1016/j.jcyt.2012.09.005

[121] Okano, H., Ogawa, Y., Nakamura, M., Kaneko, S., Iwanami, A. and Toyama, Y. (2003) Transplantation of Neural Stem Cells into the Spinal Cord after Injury. *Seminars in Cell & Developmental Biology*, **14**, 191-198. https://doi.org/10.1016/s1084-9521(03)00011-9

[122] Rodriguez, R., Rubio, R. and Menendez, P. (2011) Modeling Sarcomagenesis Using Multipotent Mesenchymal Stem Cells. *Cell Research*, **22**, 62-77. https://doi.org/10.1038/cr.2011.157

[123] Shen, Y., Wang, Y., Cheng, X., Yang, X. and Wang, G. (2023) Autophagy Regulation Combined with Stem Cell Therapy for Treatment of Spinal Cord Injury. *Neural Regeneration Research*, **18**, 1629-1636. https://doi.org/10.4103/1673-5374.363189

[124] Quertainmont, R., Cantinieaux, D., Botman, O., Sid, S., Schoenen, J. and Franzen, R. (2012) Mesenchymal Stem Cell Graft Improves Recovery after Spinal Cord Injury in Adult Rats through Neurotrophic and Pro-Angiogenic Actions. *PLOS ONE*, **7**, e39500. https://doi.org/10.1371/journal.pone.0039500

[125] Li, C., Luo, Y. and Li, S. (2024) The Roles of Neural Stem Cells in Myelin Regeneration and Repair Therapy after Spinal Cord Injury. *Stem Cell Research & Therapy*, **15**, Article No. 204. https://doi.org/10.1186/s13287-024-03825-x

[126] Phinney, D.G. and Pittenger, M.F. (2017) Concise Review: MSC-Derived Exosomes for Cell-Free Therapy. *Stem Cells*, **35**, 851-858. https://doi.org/10.1002/stem.2575

[127] Riazifar, M., Pone, E.J., Lötvall, J. and Zhao, W. (2017) Stem Cell Extracellular Vesicles: Extended Messages of Regeneration. *Annual Review of Pharmacology and Toxicology*, **57**, 125-154. https://doi.org/10.1146/annurev-pharmtox-061616-030146

[128] Park, H., Chugh, R.M., Seok, J., Cetin, E., Mohammed, H., Siblini, H., *et al.* (2023) Comparison of the Therapeutic Effects between Stem Cells and Exosomes in Primary Ovarian Insufficiency: As Promising as Cells but Different Persistency and Dosage. *Stem Cell Research & Therapy*, **14**, Article No. 165. https://doi.org/10.1186/s13287-023-03397-2

[129] Luo, Y., He, Y., Wang, Y., Xu, Y. and Yang, L. (2023) Adipose-Derived Mesenchymal Stem Cell Exosomes Ameliorate Spinal Cord Injury in Rats by Activating the Nrf2/ho-1 Pathway and Regulating Microglial Polarization. *Folia Neuropathologica*, **61**, 326-335. https://doi.org/10.5114/fn.2023.130455

[130] Akhlaghpasand, M., Tavanaei, R., Hosseinpoor, M., Yazdani, K.O., Soleimani, A., Zoshk, M.Y., *et al.* (2024) Safety and Potential Effects of Intrathecal Injection of Allogeneic Human Umbilical Cord Mesenchymal Stem Cell-Derived Exosomes in Complete Subacute Spinal Cord Injury: A First-in-Human, Single-Arm, Open-Label, Phase I Clinical Trial. *Stem Cell Research & Therapy*, **15**, Article No. 264. https://doi.org/10.1186/s13287-024-03868-0

[131] Chen, M., Lin, Y., Guo, W. and Chen, L. (2024) BMSC-Derived Exosomes Carrying miR-26a-5p Ameliorate Spinal Cord Injury via Negatively Regulating EZH2 and Activating the BDNF-TrkB-CREB Signaling. *Molecular Neurobiology*, **61**, 8156-8174. https://doi.org/10.1007/s12035-024-04082-y

[132] Chang, Q., Hao, Y., Wang, Y., Zhou, Y., Zhuo, H. and Zhao, G. (2021) Bone Marrow

Mesenchymal Stem Cell-Derived Exosomal Microrna-125a Promotes M2 Macrophage Polarization in Spinal Cord Injury by Downregulating Irf5. *Brain Research Bulletin*, **170**, 199-210. https://doi.org/10.1016/j.brainresbull.2021.02.015

[133] Wang, L., Pei, S., Han, L., Guo, B., Li, Y., Duan, R., *et al.* (2018) Mesenchymal Stem Cell-Derived Exosomes Reduce A1 Astrocytes via Downregulation of Phosphorylated NF-κB P65 Subunit in Spinal Cord Injury. *Cellular Physiology and Biochemistry*, **50**, 1535-1559. https://doi.org/10.1159/000494652

[134] Abbas, A., Huang, X., Ullah, A., Luo, L., Xi, W., Qiao, Y., *et al.* (2024) Enhanced Spinal Cord Repair Using Bioengineered Induced Pluripotent Stem Cell-Derived Exosomes Loaded with miRNA. *Molecular Medicine*, **30**, Article No. 168. https://doi.org/10.1186/s10020-024-00940-6

[135] Zhang, T., Gao, K., Yan, T., Lyu, C. and Lyu, C. (2021) Potential Therapeutic Mechanism of Traditional Chinese Medicine Monomers on Neurological Recovery after Spinal Cord Injury. *Chinese Medical Journal*, **134**, 1681-1683. https://doi.org/10.1097/cm9.0000000000001476

[136] Luo, D., Li, X., Hou, Y., Hou, Y., Luan, J., Weng, J., *et al.* (2021) Sodium Tanshinone IIA Sulfonate Promotes Spinal Cord Injury Repair by Inhibiting Blood Spinal Cord Barrier Disruption *in Vitro* and *in Vivo*. *Drug Development Research*, **83**, 669-679. https://doi.org/10.1002/ddr.21898

[137] Tang, H., Guo, Y., Zhao, Y., Wang, S., Wang, J., Li, W., *et al.* (2020) Effects and Mechanisms of Acupuncture Combined with Mesenchymal Stem Cell Transplantation on Neural Recovery after Spinal Cord Injury: Progress and Prospects. *Neural Plasticity*, **2020**, Article ID: 8890655. https://doi.org/10.1155/2020/8890655

[138] Zhang, X.-F., Zou, Y., Zhao, Y., Wang, T.-H. and Zhang, W. (2012) Effects of Electroacupuncture of "Governor Vessel" Acupoints on Changes of BDNF in the Cortical Motor Area of Mice with Spinal Cord Transection. *Journal of Sichuan University. Medical Science Edition*, **43**, 250-253.

[139] Huang, Y., Zhu, N., Chen, T., Chen, W., Kong, J., Zheng, W., *et al.* (2019) Triptolide Suppressed the Microglia Activation to Improve Spinal Cord Injury through miR-96/IKKβ/NF-κB Pathway. *Spine*, **44**, E707-E714. https://doi.org/10.1097/brs.0000000000002989

[140] Li, X., Wu, P., Yao, J., Zhang, K. and Jin, G. (2022) Genistein Protects against Spinal Cord Injury in Mice by Inhibiting Neuroinflammation via Tlr4-Mediated Microglial Polarization. *Applied Bionics and Biomechanics*, **2022**, Article ID: 4790344. https://doi.org/10.1155/2022/4790344

[141] Yang, P., Chen, A., Qin, Y., Yin, J., Cai, X., Fan, Y., *et al.* (2019) Buyang Huanwu Decoction Combined with BMSCs Transplantation Promotes Recovery after Spinal Cord Injury by Rescuing Axotomized Red Nucleus Neurons. *Journal of Ethnopharmacology*, **228**, 123-131. https://doi.org/10.1016/j.jep.2018.09.028

[142] Ding, Y., Yan, Q., Ruan, J., Zhang, Y., Li, W., Zeng, X., *et al.* (2011) Bone Marrow Mesenchymal Stem Cells and Electroacupuncture Downregulate the Inhibitor Molecules and Promote the Axonal Regeneration in the Transected Spinal Cord of Rats. *Cell Transplantation*, **20**, 475-491. https://doi.org/10.3727/096368910x528102

[143] Liu, H., Yang, K., Xin, T., Wu, W. and Chen, Y. (2012) Implanted Electro-Acupuncture Electric Stimulation Improves Outcome of Stem Cells' Transplantation in Spinal Cord Injury. *Artificial Cells, Blood Substitutes, and Biotechnology*, **40**, 331-337. https://doi.org/10.3109/10731199.2012.659350

[144] Yu, X., Chen, J., Liu, M., Li, Y., Jia, Y., Zhan, H., *et al.* (2024) Meta-Analysis of the Curative Effect of Sacral Nerve Magnetic Stimulation on Neurogenic Bladder after

Spinal Cord Injury. *Medicine*, **103**, e40150.
https://doi.org/10.1097/md.0000000000040150

[145] Ning, G., Song, W., Xu, H., Zhu, R., Wu, Q., Wu, Y., *et al.* (2018) Bone Marrow Mesenchymal Stem Cells Stimulated with Low-Intensity Pulsed Ultrasound: Better Choice of Transplantation Treatment for Spinal Cord Injury: Treatment for SCI by LIPUS-BMSCs Transplantation. *CNS Neuroscience & Therapeutics*, **25**, 496-508.
https://doi.org/10.1111/cns.13071

[146] Liao, Y., Chen, M., Chen, S., Luo, K., Wang, B., Ao, L., *et al.* (2022) Low-Intensity Focused Ultrasound Alleviates Spasticity and Increases Expression of the Neuronal K-Cl Cotransporter in the L4-L5 Sections of Rats Following Spinal Cord Injury. *Frontiers in Cellular Neuroscience*, **16**, Article ID: 882127.
https://doi.org/10.3389/fncel.2022.882127

[147] Jeon, J., Park, S.H., Choi, J., Han, S.M., Kim, H., Shim, S.R., *et al.* (2024) Association between Neural Stem/progenitor Cells and Biomaterials in Spinal Cord Injury Therapies: A Systematic Review and Network Meta-analysis. *Acta Biomaterialia*, **183**, 50-60. https://doi.org/10.1016/j.actbio.2024.06.011

[148] Chen, M., Xu, G., Guo, W., Lin, Y. and Yao, Z. (2024) Bilobalide Activates Autophagy and Enhances the Efficacy of Bone Marrow Mesenchymal Stem Cells on Spinal Cord Injury via Upregulating FMRP to Promote WNK1 mRNA Decay. *Neurochemical Research*, **50**, Article No. 33. https://doi.org/10.1007/s11064-024-04287-6

[149] Pai, V., Singh, B.N. and Singh, A.K. (2024) Insights into Advances and Applications of Biomaterials for Nerve Tissue Injuries and Neurodegenerative Disorders. *Macromolecular Bioscience*, **24**, e2400150. https://doi.org/10.1002/mabi.202400150

[150] Tang, Z., Ye, Y., Yang, K., Guo, X., Gao, X., Wu, C., *et al.* (2024) Experimental Study of cbmmsc Based on Nanosilver Hydrogel Nerve Conduit for Repairing Spinal Cord Injury. *Journal of Cellular and Molecular Medicine*, **28**, e70149.
https://doi.org/10.1111/jcmm.70149

[151] Xu, J., Cheng, S., Jiao, Z., Zhao, Z., Cai, Z., Su, N., *et al.* (2019) Fire Needle Acupuncture Regulates Wnt/ERK Multiple Pathways to Promote Neural Stem Cells to Differentiate into Neurons in Rats with Spinal Cord Injury. *CNS & Neurological Disorders—Drug Targets*, **18**, 245-255.
https://doi.org/10.2174/1871527318666190204111701

[152] Bradshaw, K.J. and Leipzig, N.D. (2024) Applications of Regenerative Tissue-Engineered Scaffolds for Treatment of Spinal Cord Injury. *Tissue Engineering Part A*.
https://doi.org/10.1089/ten.tea.2024.0194