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Article

Mesenchymal stem cells applications in spinal cord injury

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Abstract: Spinal cord injury (SCI) is a severe functional impairment of the limbs caused by direct or indirect external factors. The consequences of SCI can be extensive, encompassing the partial loss of sensation, movement, and sphincter function. This is attributable to the loss of neurons, an inflammatory response, and immune cell infiltration. SCI can result in long-term physical and psychological harm to patients, as well as imposing a significant economic burden on the entire society. Mesenchymal stem cells (MSCs) are a type of pluripotent stem cell that exhibits both self-renewal and multipotent differentiation abilities. They possess the anti-inflammatory properties, immunoregulatory abilities, and the capacity for neural and vascular regeneration ability, collectively rendering them a promising candidate for the treatment of SCI. In this review, we provide a comprehensive overview of the preclinical and clinical applications of MSCs in SCI and the underlying mechanisms, discuss the limitations of MSC application in SCI and the possible solutions, hope to provide some useful insights for the scientists.

Keywords: spinal cord injury; mesenchymal stem cells; preclinical and clinical application

1. Introduction

Spinal cord injury (SCI) is defined as damage to the spinal cord that can be caused by traumatic or non-traumatic means, including falls, road traffic accidents, and violence. SCI can be classified into two main categories: primary and secondary SCI. Primary SCI is a kind of damage caused by external forces acting on the spinal cord directly or indirectly, the degree and clinical manifestations depend on the location and nature of the primary injury [1]; secondary SCI is a damage not directly caused by external forces, it is mainly permanent damage to residual normal nerve tissue on the basis of primary SCI. This is due to vertebral fracture displacement and delayed release of hematoma compression. The mechanisms of damage are diverse, including vascular mechanisms, biochemical mechanisms, and cell apoptosis [2,3].

The injury can result in the complete or incomplete loss of sensation and/or motor function at the site of injury, the degree of SCI-related disorders depends on the severity and location of the injury [4,5]. Common secondary complications of SCI include chronic pain, deep vein thrombosis, urethral infection, bedsores, and respiratory complications. These secondary complications of SCI can further threaten the life of patients; and improper management of SCI and SCI-related secondary complications often leads to premature death [6].

SCI has a relatively large patient population and a distinctive set of disease characteristics. Statistical data from 204 countries and territories demonstrated that there were approximately 20.6 million individuals were living with SCI worldwide

in 2019. Furthermore, the global prevalence, global incidence, and years of life lived with disability (YLDs) increased by 81.5%, 52.7%, and 65.4%, respectively, from 1990 to 2019. It is notable that the higher incidence rate, prevalence rate, and YLDs of SCI were observed in males compared to females [7]. Similarly, in China, the incidence rate of SCI was reported to be between14.6 and 60.6 per million, with a male-to-female ratio of 3.1:1 [8,9]. A recent statistical data revealed that there were approximately 0.76 million individuals with traumatic SCI in China, with an annual increase of 0.07 million patients. This has resulted in an enormous mental and economic burden on patients and society [10].

Mesenchymal stem cells (MSCs) are a type of adult stem cell that can be found in a number of different tissues, including bone marrow [11], umbilical cord [12], placental tissue [13], and adipose tissue [14]. They are capable of differentiating into a number of cell types and can secrete a variety of cytokines, which enables them to participate in the repair of tissue injuries and the treatment of various diseases [15–18]. The characteristics of MSCs, including their ease of isolation from multiple human tissues, their immunomodulatory effect [19], and their low immunogenicity [20]. The clinical application of these cells has been enabled by the use of MSCs in the treatment of a range of diseases, including cardiovascular diseases [21], neurological disorders [22], and autoimmune diseases [23]. Recent evidence has demonstrated that MSCs can differentiate into neurons [24,25] and oligodendrocytes [26], and secrete multiple kinds of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and nerve growth factor (NGF) [27,28]. Furthermore, they have been demonstrated to have an immunomodulatory effect [29], which makes them a promising candidate for application in SCI. This review will present a summary of the recent preclinical and clinical applications of MSCs in SCI, along with an analysis of the regulatory mechanisms and application limitations. The aim is to provide guidance for the future applications of MSCs in SCI.

2. Basic characteristics of MSCs

MSCs represent the most prominent members of the stem cell family. To date, scientists have isolated MSCs from various different human tissues, including bone marrow, umbilical cord, umbilical cord blood, teeth, adipose tissue [30,31], and menstrual blood [32]. These cells are characterized by the expression of CD105, CD73, and CD90, and they merely express CD45, CD34, CD14, CD19, and HLA DR on their surface; and the notable differences in the expression of surface markers have been observed among different types of MSCs [33,34]. Especially, MSCs have been observed to express a lower level of the major histocompatibility complex (MHC-I) and to lack the expression of co-stimulatory molecules of T cells on their surface, including MHC-II, CD40, and CD40L. This prevents the generation of the second signal of MSCs, which could otherwise result in immune rejection following allogeneic transplantation [35]. MSCs possess the capacity for self-renewal throughout their lifetime within the body. They demonstrate robust proliferative abilities, resulting in an increase in the number of MSCs both in vivo and in vitro through the utilization of symmetric and asymmetric cell division mechanisms. The

evidence demonstrated that MSCs can be passaged up to 40 times in vitro while maintaining the elevated cell activity and pluripotency [36]. The passage of MSCs may exert an influence on the characteristics of these cells. For example, Crisostomo, Paul R, et al. observed that MSCs derived from rats and passaged three times exhibited elevated levels of vascular endothelial growth factor (VEGF) release in comparison to the passage 5 and passage 10 MSCs; furthermore, the passage 5 and passage 10 MSCs demonstrated a diminished efficacy in an ischemia/reperfusion model [37]. Qinjun Zhao, et al. compared the immunomodulating capacities of different passages of UC-MSCs, found that there were no the significant differences at the levels of morphology, biomarker expression, and cytokine secretion among the different passages of UC-MSCs. However, the passages of UC-MSCs were observed to facilitate the adipogenic differentiation and cell apoptosis [38]. Shan Wang, et al. examined the genomic profiles of MSCs at passages (P) 4, 6, 8, 10, and 12, they observed notable difference in the expressions of mRNAs, long noncoding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs between MSCs at P4 and P12. Such differences may impact the proliferation, differentiation, and immunoregulatory functions of MSCs [39].

MSCs are a group of undifferentiated cells with the potential to differentiate into various kinds of body cells under the specific conditions. Additionally, MSCs are capable of secreting extracellular vesicles, a range of growth factors (vascular endothelial growth factor, basic fibroblast growth factor, insulin-like growth factors) and transcription factors (ICAM1, SMAD3, MAPK, TGF-β), which collectively demonstrate potential in the field of disease applications. For example, Chunling Xue, et al. provided the evidence that exosomes derived from MSCs could stimulate the expression of ICAM1 in human brain microvascular endothelial cells (HBMECs) to promote the angiogenesis in a mouse Parkinson's disease model [40]; Yan Zhang, et al, found that umbilical cord blood mesenchymal stem cells (UCB-MSCs) and UCB-MSCs-exosomes could accelerate the skin regeneration and cell proliferation, promote the collagen fibers distribution by regulating the expression of transforming growth factor-β (TGF-β) [41].

Immune regulation represents the physiological function of the body that enables the recognition and elimination of antigenic foreign substances, thereby maintaining the physiological dynamic balance and relative stability [42]. MSCs are a type of undifferentiated cell with low immunogenicity. This is due to the fact that MSCs express a lower level of MHC I and are unable to express MHC II, which results in a characteristic of immune exemption. Furthermore, MSCs possess immune regulatory mechanisms that pertain to both innate and acquired immunity. The available evidence demonstrated that MSCs are capable of expressing a range of immune modulators, which play a pivotal role in the immune regulation of these cells [43]. Ruiqi Yu, et al. identified that cullin 4B (CUL4B) regulated the pro-inflammatory cytokines, thereby activating the immunosuppressive capacity of MSCs. Specifically, a high level of inducible nitric oxide synthase (iNOS) was observed to enhance the immunosuppressive capacity of MSCs when these cells did not express cullin 4B; the CUL4B-RING E3 ligase (CRL4B) complex inhibited the transcription of Dlx1 and Pmepa1 by cooperating with the PRC2 complex and HDACs, thereby demonstrating a CUL4B-mediated immunosuppressive capacity of

MSCs [44]. Chih-Yu et al. [45] demonstrated that transforming growth factor-β1(TGF-β1) in adipose-derived mesenchymal stem cells (ASCs) enhanced the secretion of interleukin-6 (IL-6), t thereby regulating the M2 macrophage polarization, and alleviating the symptoms of a dialysis-induced peritoneal fibrosis model. Jayeeta Giri et al. [46] demonstrated that chemokine ligand 2 (CCL2) and C-X-C motif chemokine 12 (CXCL12) derived from MSCs exhibited a synergistic effect on the polarization of tissue macrophages in a gut injury model (**Figure 1**).

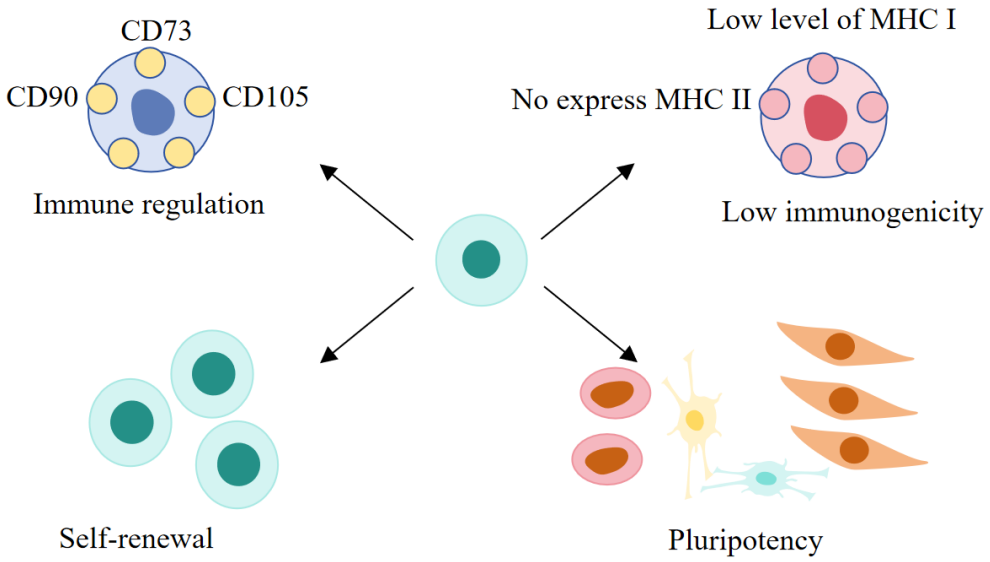

Figure 1. The basic characteristics of MSCs.

3. The preclinical application of MSCs in SCI

Table 1. The summary of the recent applications of MSCs in SCI.

MSCs type	Animal species	Modeling method	Administration method	Therapeutic effect	Mechanism	Reference
hUCMSCs	mouse	mechanical induced SCI	stereotaxic microinjection	promote functional recovery	attenuate neuronal ferroptosis	[47]
hUCMSCs	rat	mechanical induced SCI	caudal vein injection	repair nerve tissue	regulate KDM6A/NOX4 axis	[48]
hUCMSCs	rat	mechanical induced SCI	stereotaxic microinjection	promote the GABAAR subunits	regulate BDNF secretion	[49]
hUCMSCs-EVs	rat	mechanical induced SCI	stereotaxic microinjection	promote intervertebral disc regeneration	activate Mir-7-5p/NF-κB/CXCL2 Axis	[50]
BMMSCs-Exos	rat	mechanical induced SCI	tail vein injection	promote axonal regeneration	regulate PTEN/AKT/mTOR	[51]
hUCMSCs	rat	mechanical induced SCI	subarachnoid transplantation	improve lesion size and locomotion	/	[52]
Epidural fat-MSCs	rat	mechanical induced SCI	tail vein injection	improve functional recovery	inhibition of NLRP3	[53]

Table 1. (*Continued*).

MSCs type	Animal species	Modeling method	Administration method	Therapeutic effect	Mechanism	Reference
hUCMSCs	rat	mechanical induced SCI	intrathecal implantation	restore of the GABA	/	[54]
hUCMSCs	mouse	mechanical induced SCI	stereotaxic microinjection	improve the mechanical hyperalgesia	/	[55]
human placenta-MSCs	mouse	mechanical induced SCI	stereotaxic injection	improve the functional recovery	/	[56]
MSCs	rat	mechanical induced SCI	tail vein injection	improve the functional recovery	regulate miR-329-3p/IGF1R axis	[57]
BMMSCs	rat	mechanical induced SCI	tail vein injection	reduce inflammation	regulate TLR4/NF-κB	[58]
human placenta-MSCs	rat	mechanical induced SCI	intrathecal injection	promote locomotor and sensory function	/	[59]
BMMSCs- EVs	rat	mechanical induced SCI	tail vein injection	promote microvascular stabilization and functional recovery	regulate TGF-β	[60]
BMMSCs-EVs	rat	mechanical induced SCI	tail vein injection	enhance functional recovery	regulate miR-21/JAK2/STAT3	[61]
hUCMSCs	mouse	mechanical induced SCI	/	improve functional recovery	inhibit canonical notch ligand 4	[62]
all-trans retinoic acid-BMMSCs	rat	mechanical induced SCI	tail vein injection	improve motor function	regulate HMGB1/NF-κB/NLRP3	[63]
hUCMSCs-EVs	rat	mechanical induced SCI	tail vein injection	promote functional recovery	Activate the BDNF-TrkB-CREB	[64]
hUCMSCs	mouse	mechanical induced SCI	stereotaxic injection	promote neuron survival and myelin repair	regulate PTBP-1 and TNF-α/NF-κB	[65]
bFGF-hUCMSCs	mouse	mechanical induced SCI	tail intravenous injection	promote locomotion functional recovery	regulate PI3K-Akt-GSK3β	[66]
Wharton's jelly MSCs-Exos	rat	mechanical induced SCI	intrathecal administration	promote locomotion functional recovery	/	[67]
hypoxia-preconditioned BMMSCs-EVs	rat	mechanical induced SCI	subcutaneously injection	reduced the lesion area and inflammation	regulate the Irak1/Traf6/NF-κB	[68]
BMMSCs-EVs	rat	mechanical induced SCI	tail vein injection	improve nerve function recovery	/	[69]
Rat UCMSCs	rat	mechanical induced SCI	intravenous injection	improve motor function	/	[70]
hUCMSCs	rat	mechanical induced SCI	stereotaxic injection	promote the injury repair	/	[71]
hUCMSCs	mouse	mechanical induced SCI	stereotaxic injection	enhance the injury repair	/	[72]
human amniotic fluid MSCs	rat	mechanical induced SCI	stereotaxic injection	promote functional recovery	/	[73]
olfactory mucosa-MSCs	mouse	mechanical induced SCI	stereotaxic injection	repair spinal cord injury	regulate microglial polarization	[74]

Given their excellent characteristics, MSCs have also yielded considerable outcomes in the application of SCI. The evidence suggests that distinct types of MSCs or their derivatives have been shown to exert beneficial therapeutic effects in SCI models. For example, Senyu Yao, et al. demonstrated that the administration of MSCs could significantly improve the motor deficits within seven days through mitochondrial transfer, thereby attenuating neuronal ferroptosis by regulating the mitochondrial quality control (MQC) process [47]. And Yuyong Chen, et al. investigated the impact of miR-26a-modified exosomes on SCI, found that these special exosomes could promote axonal regeneration and attenuate glial scarring in SCI rats by regulating AKT/mTOR pathways [51]; Junhao Deng, et al. obtained the MSCs-derived spheroids by hanging-drop method, these spheroids could secrete the anti-inflammatory factors and trophic factors, exhibited the effects of inflammation, astrogliosis, and promoting angiogenesis in SCI model [56].

In order to gain the further insight into the preclinical application of MSCs in SCI, we conducted a comprehensive literature search in the PubMed database, found that seven distinct types of MSCs have been applied in SCI models, including hUCMSCs, BMMSCs, human placenta-MSCs, Wharton's jelly MSCs, human amniotic fluid MSCs, epidural fat-MSCs, and olfactory mucosa-MSCs; the application forms included gene-modified or drug-pretreated stem cells, external vesicles, and exosomes; the SCI modeling method was a mechanical-induced SCI; the administration method of MSCs mainly included stereotaxic microinjection and tail vein injection (**Table 1**).

Abbreviations: SCI, spinal cord injury; MSCs, mesenchymal stem cells; hUCMSCs, human umbilical cord mesenchymal stem cells; BMMSCs, bone marrow mesenchymal stem cells; EVs, external vesicles; Exos, exosomes; bFGF, base fibroblast growth factor; KDM6A, lysine-specific demethylase 6A; NOX4, NADPH oxidase 4; BDNF, brain-derived neurotrophic factor; NF-κB, nuclear factor kappa-B; CXCL2, C-X-C Motif Chemokine Ligand 2; PTEN, phosphatase and tensin homolog deleted on chromosome ten; AKT, protein kinase B; mTOR, mammalian target of rapamycin; NLRP3, NOD-like receptor thermal protein domain-associated protein 3; IGF1R, Insulin-like growth factor 1; TLR4, toll-like receptor 4; TGF-β, tumor growth factor-β; JAK2, janus kinase 2; STAT3, signal transducer and activator of transcription 3; HMGB1, high mobility group box-1 protein; TrkB, tropomyosin receptor kinase B; CREB, cAMP-response element binding protein;PTBP1, polypyrimidine tract binding protein 1; GSK3, glycogen synthase kinase 3; Irak1, IL-1 receptor associated kinase; Traf6, tumor necrosis factor receptor-associated factor 6.

The summary data demonstrated that numerous signaling pathways are involved in regulating the therapeutic effects of MSCs on SCI, including lysine-specific demethylase 6A/ NADPH oxidase 4 (KDM6A/NOX4), Mir-7-5p/nuclear factor kappa-B/C-X-C Motif Chemokine Ligand 2 (Mir-7-5p/NF-κB/CXCL2), phosphatase and tensin homolog deleted on chromosome ten/protein kinase B/mammalian target of rapamycin (PTEN/AKT/mTOR), toll-like receptor 4/nuclear factor kappa-B (TLR4/NF-κB), high mobility group box-1 protein/nuclear factor kappa-B/NOD-like receptor thermal protein domain-associated protein 3

(HMGB1/NF-κB/NLRP3), and IL-1 receptor associated kinase/tumor necrosis factor receptor-associated factor 6/NF-κB (Irak1/Traf6/NF-κB) (**Figure 2**).

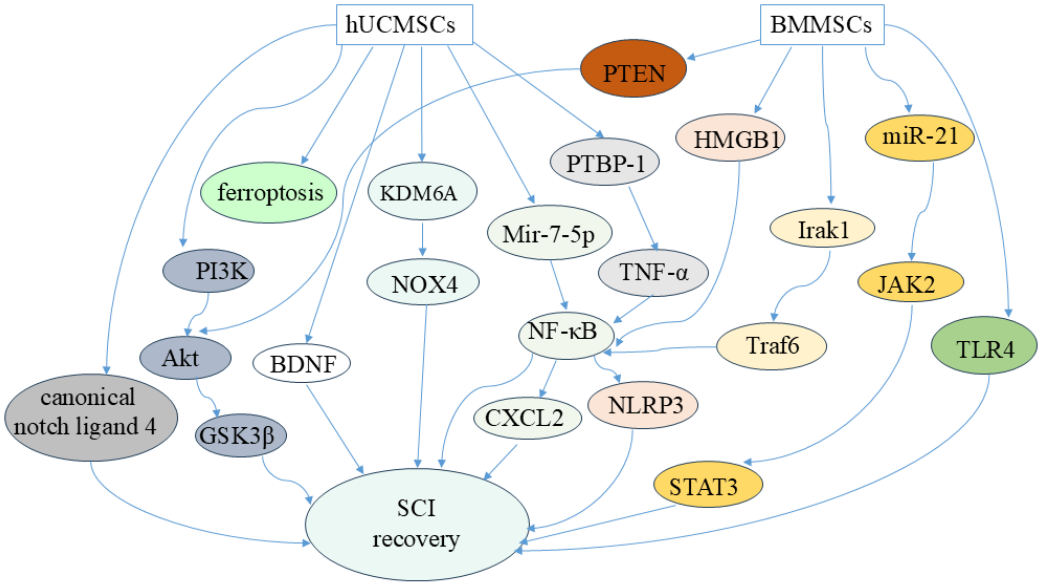

Figure 2. The summary of the underlying mechanisms of MSCs treatment on SCI.

Abbreviations: SCI, spinal cord injury; hUCMSCs, human umbilical cord mesenchymal stem cells; BMMSCs, bone marrow mesenchymal stem cells; KDM6A, lysine-specific demethylase 6A; NOX4, NADPH oxidase 4; BDNF, brain-derived neurotrophic factor; NF-κB, nuclear factor kappa-B; CXCL2, C-X-C Motif Chemokine Ligand 2; PTEN, phosphatase and tensin homolog deleted on chromosome ten; AKT, protein kinase B; mTOR, mammalian target of rapamycin; NLRP3, NOD-like receptor thermal protein domain-associated protein 3; TLR4, toll-like receptor 4; TGF-β, tumor growth factor-β; JAK2, janus kinase 2; STAT3, signal transducer and activator of transcription 3; HMGB1, high mobility group box-1 protein; TrkB, tropomyosin receptor kinase B; CREB, cAMP-response element binding protein; PTBP1, polypyrimidine tract binding protein 1; GSK3, glycogen synthase kinase 3.

4. The clinical application of MSCs in SCI

In consequence of the rapid development of basic research and the superior performance of MSCs, a number of countries are actively promoting the research and transformation of MSCs through multiple policies. A review of the PubMed database demonstrated that 16 clinical trials investigating the use of MSCs in SCI have been conducted in the recent years. These trials spanned a range of phases, including 10 Phase I, 2 Phase II, 3 Phase I/II, and 1 Phase III trial; the main MSCs types are BMMSCs, NSCs, UCMSCs, and Wharton jelly-MSCs; the administration methods include stereotactic injection, stereotactic injection, intramedullary free-hand transplantation, and repeated subarachnoid administration. Furthermore, five clinical trials have documented the occurrence of the mild adverse effects during the course of the trials (**Table 2**). These clinical trials effectively elucidate the

therapeutic effect, adverse effects, and the absorption, distribution, metabolism, and excretion of MSCs, to determine the efficacy and safety of MSCs.

Table 2. The summary of the clinical applications of MSCs in SCI.

Clinical stage	MSCs type	Country	Trial period	Administration	Therapeutic effect	Adverse effect	Reference
Phase I trial	ADMSCs	USA	12 months	intrathecal delivery	improvement in AIS grade	headaches, musculoskeletal symptoms	[75]
Phase I trial	NSCs	USA	12 months	stereotactic injection	neurological improvement	not mentioned	[76]
Phase I trial	BMMSCs	USA	12 weeks	stereotactic injection	improvement in AIS grade	not mentioned	[77]
Phase I trial	BMMSCs	India	6 months	intramedullary route	decrease spasticity and improve posture control	not mentioned	[78]
Phase I trial	hUCMSC-exos	Iran	12 months	intrathecal injection	promote functional improvement	not observed	[79]
Phase I trial	hUCBMSCs	Russian	12 months	intrathecal injection	promote functional restoration	mild symptoms	[80]
Phase I trial	BMMSCs	Iran	24 months	stereotactic injection	promote functional ability	mild symptoms	[81]
Phase I trial	MSCs	Spain	10 months	intrathecal injection	promote functional ability	not observed	[82]
Phase II trial	MSCs	Japan	6 months	intrathecal injection	promote neurologic improvement	not mentioned	[83]
Phase I trial	NSCs	USA	12 months	intramedullary free-hand transplantation	promote neurologic improvement	serious adverse events were found	[84]
Phase I trial	Wharton jelly-MSCs	Spain	6 months	intrathecal injection	promote sensory improvement	not mentioned	[85]
Phase II trial	NSCs	USA	24 months	intrathecal injection	promote functional improvement	not mentioned	[86]
Phase III trial	MSCs	Korea	12 months	stereotactic injection	promote neurological improvement	not observed	[87]
Phase I/II trial	BMMSCs and UCMSCs	Jordan	12 months	intrathecal injection	promote ASIA scores	headaches and back pain	[88]
Phase I/II trial	hNSPCs	Korea	12 months	stereotactic injection	promote neurological improvement	not observed	[89]
Phase I/II trial	MSCs	Spain	12 months	repeated subarachnoid administration	promote motor function	not mentioned	[90]

Abbreviations: MSCs, mesenchymal stem cells; hUCMSCs, human umbilical cord mesenchymal stem cells; BMMSCs, bone marrow mesenchymal stem cells; NSCs, neural stem cells; hNSPCs, human neural stem and progenitor cells; AIS grade, abbreviated injury scale grade; ASIA scores, American spinal injury association scores.

5. Application limitations and prospects of MSCs in SCI

MSCs are a type of cell that possess the capacity for self-renewal and differentiation into multiple cell lineages. In specific circumstances, they are capable of differentiating into various types of tissue cells. In fact, MSCs necessitate a

combination of growth factors and nutrients to maintain differentiation and development. The absence of standardization and diversity in stem cell sources has resulted in the development of multiple methods for culturing MSCs. These cultivation methods employ varying levels of growth factors and nutrients, which have a significant impact on the stemness and proliferation ability of MSCs. It is imperative that a standardized methodology for the cultivation of MSCs be developed in order to facilitate their wider application in the context of SCI. Currently, the predominant modeling method for SCI is mechanically induced SCI, encompassing models that utilize strike, compression, transection, and traction, these models are effective in simulating the pathogenesis and mechanisms of SCI in clinical practice to a large degree, However, they exhibit inconsistencies in the degree of damage and poor repeatability. Addressing these issues is of paramount importance for the application of MSCs in SCI. A review of the clinical data indicates that the administration of MSCs can be achieved through two main methods: stereotactic injection and intrathecal injection. These methods facilitate the rapid delivery of MSCs to the lesion site, where they can exert their therapeutic effects. Nevertheless, the procedure is arduous and may cause significant discomfort to the patient. Moreover, the potential for infection exists with repeated punctures. The development of painless alternative administration methods is of great urgency.

The recent advancement of biological therapy techniques, including photobiological regulation, T-cell immunotherapy, and bioactive materials, has been observed to exhibit targeting specificity and remarkable therapeutic efficacy, which may potentially render them an optimal therapeutic approach for SCI.

6. Conclusion

MSCs represent a promising avenue of cell therapy, with significant advancements in the application of MSCs in spinal cord injury (SCI) research, both at the preclinical and clinical levels. Once the aforementioned limitations have been addressed, including the lack of a standardized method for culturing MSCs, the development of a more reliable SCI model and the introduction of painless alternative administration methods, the prospects for the use of MSCs in SCI will undoubtedly improve.

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