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REVIEW

Regulatory Role of Mesenchymal Stem Cells on Secondary Inflammation in Spinal Cord Injury

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Abstract: Spinal cord injury (SCI) is a catastrophic condition with high morbidity and mortality that still lacks effective therapeutic strategies. It is well known that the most important stage in SCI pathogenesis is secondary injury, and among the involved mechanisms, the inflammatory cascade is the main contributor and directly influences neurological function recovery. In recent years, increasing evidence has shown that mesenchymal stem cells (MSCs) transplantation is a promising immunomodulatory strategy. Transplanted MSCs can regulate macrophage-, astrocyte-, and T lymphocyte-mediated neuroinflammation and help create a microenvironment that facilitates tissue repair and regeneration. This review focuses on the effects of different types of immune cells and MSCs, specifically the immunoregulatory capacity of MSCs in SCI and repair. We will also discuss how to exploit MSCs transplantation to regulate immune cells and develop novel therapeutic strategies for SCI.

Keywords: spinal cord injury, mesenchymal stem cells, immune cells, neuroinflammation, immunoregulation, macrophage, astrocyte, T cell

Introduction

Spinal cord injury (SCI) is a potentially devastating event in the central nervous system (CNS) that can lead to the loss of sensory and motor functions below the damaged segment with huge burdens on patients, their families, and society due to the high treatment cost.[1,2] The global rate of traumatic SCI ranges from 250,000 to 500,000 people annually and will gradually climb with the growing number of people using modern transportation along with aging populations.[3,4] SCI triggers a sequential set of pathophysiological processes that can be classified as primary and secondary injury.[5] Acute primary injury commonly occurs due to the mechanical insult, which can be caused by laceration, contusion, compression, or transection.[6,7] These events severely disrupt neuronal pathways and axonal networks, cause hemorrhage, and compromise the blood-spinal cord barrier (BSCB).[8,9] It is widely believed that the most important phase is secondary injury, which develops a few minutes after the initial injury. It consists of a series of auto-destructive cellular and molecular changes, such as inflammatory response, glial scar formation, edema, thrombosis, free radical release, and apoptotic and necrotic cells death.[10,11] Among the mechanisms of secondary injury, a robust and chronic inflammatory response has been observed at the injury epicenter and in surrounding areas.[12,13] Studies have demonstrated that this response can contribute to a wide range of inflammatory and autoimmune disorders that exacerbate lesion progression and hamper neurological function recovery.[13,14] Unfortunately, there is still a lack of therapeutic methods targeting neuroinflammation; only methylprednisolone has shown efficacy and was approved by the US Food and Drug Administration for clinical treatment.[15,16] However, its use has gradually declined over the past few decades due to the serious complications related to glucocorticoid therapy, such as gastrointestinal bleeding, wound infection, pulmonary embolism, and sepsis.[17,18] Despite the controversies concerning the glucocorticoid treatment, its effects suggest that suppressing the inflammatory response after injury is a viable approach to improve the condition of SCI patients.[19,20] It is

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therefore imperative to investigate the roles of different types of immune cells on excessive neuroinflammation in order to develop new therapeutic strategies targeting neuroinflammation in the setting of SCI.

Over the past few decades, stem cell-based therapy has provided new hope for treating SCI patients.[20] Mesenchymal stem cells (MSCs) have attracted increasing attention due to their remarkable advantages of self-renewal, differentiation potential, and immunoregulation.[21] The International Society for Cellular Therapy sets a minimum standard of MSCs as follows: cells that are positive for the surface markers of cluster of differentiation (CD)73, CD90, CD29, and CD105, but not with CD14, CD45, CD34, CD11b, or human leukocyte antigen-DR; are plastic-adherent and fibroblast-like under standard culture conditions; and can differentiate into chondrocytes, adipocytes and osteoblasts in vitro.[22] Due to the low expression of costimulatory molecules and class II major histocompatibility complex, these pluripotent stem cells do not trigger an obvious immune response after transplantation.[22,23] To date, MSCs have been isolated from distinct adult tissues (eg, bone marrow, peripheral blood, adipose tissue) and neonatal tissues (eg, umbilical cord and placenta).[24,25] MSCs from different sources have been demonstrated to be effective in animal models of numerous inflammatory diseases as well as in ongoing clinical trials including SCI.[26–29] Growing evidence suggests that these multipotent cells can induce an immunosuppressive and reparative microenvironment through cell–cell interaction and a paracrine effect, thereby promoting anatomical and functional recovery after SCI.[30,31]

In this review, we summarize the roles of immune cells and transplanted MSCs with a focus on the immunomodulatory effects of MSCs in SCI and repair. We will pay special attention to the fact that preconditioning may further promote the effects of MSC-based therapy in SCI models. Adequately clarifying the contributions of different immune cells, MSCs, and their reciprocal interactions to SCI pathogenesis and repair will be of great value for developing new therapeutic approaches for SCI.

Inflammation After SCI

Although microglia can be found throughout the CNS and numerous immune cells are found in the meningeal spaces, the absence of peripheral immune cells in the normal CNS implies that the spinal cord is privileged from normal immune surveillance.[32] The BSCB consists of three main cellular components: capillary basement membrane, astrocytes, and pericytes.[33] Similar to the blood–brain barrier, the BSCB is essential for excluding peripheral immune cells and various inflammatory and toxic metabolic products from the CNS, thereby maintaining microenvironment stability.[34,35] Following SCI, cells damaged at the injury site can produce types of intracellular proteins and cell debris known as damage-associated molecular patterns (DAMPs) that act as strong inflammatory stimuli and are responsible for the excessive inflammatory response post-SCI.[36,37] DAMPs bind to pattern recognition receptors in resident inflammatory cells, including resident microglia and astrocytes, resulting in the rapid activation of these cells.[37,38] In response to neuropathology, astrocytes undergo a suite of molecular, morphological, and functional remodeling, which eventually leads to the acquisition of new functions.[39] However, the abilities of astrocyte proliferation and polarization vary with the intensity and type of stimulation after SCI. With the increasing stimulation intensity, cell hyperplasia, proliferation, migration, and alignment occur gradually, and these reactive astrocytes show a gradual up-regulation of glial fibrillary acidic protein (GFAP) and secretion of cytokines (eg, interleukin (IL)-6, transforming growth factor beta (TGF-β), IL-1β) and other molecules (eg, cyclooxygenase (COX)-2, inducible nitric oxide synthase, S100β).[39] When the BSCB is damaged, these inflammatory mediators can drive peripheral immune cells to the lesion site; they then polarize towards pro-inflammatory phenotypes and exhibit cytokine expression patterns similar to the resident inflammatory cells, resulting in a more severe local inflammatory response that consequently hinders neurological function recovery (Figure 1).[40,41] A sequential inflammatory cascade is switched on following SCI. Neutrophils are driven to the lesion site within 24 hours and facilitate phagocytosis and the removal of cellular debris; many neutrophils also secrete distinct oxidative and tissue-degrading enzymes, proteases, reactive oxygen species (ROS), and tumor necrosis factor (TNF)-α, creating a harmful microenvironment that is neurotoxicity to neurons.[14,42,43] After neutrophil infiltration, blood-derived monocytes are the next inflammatory cells to appear at the lesion site at approximately 2 days and peaking on 5–7 days.[44,45] These cells play critical roles in clearing cellular debris, promoting angiogenesis, and modulating cytokine secretion and the activation and proliferation of T lymphocytes.[46] Lymphocyte numbers are highest at 9 days and are essential for the progression or resolution of secondary damage by adopting distinct immunophenotypes.[47] The three

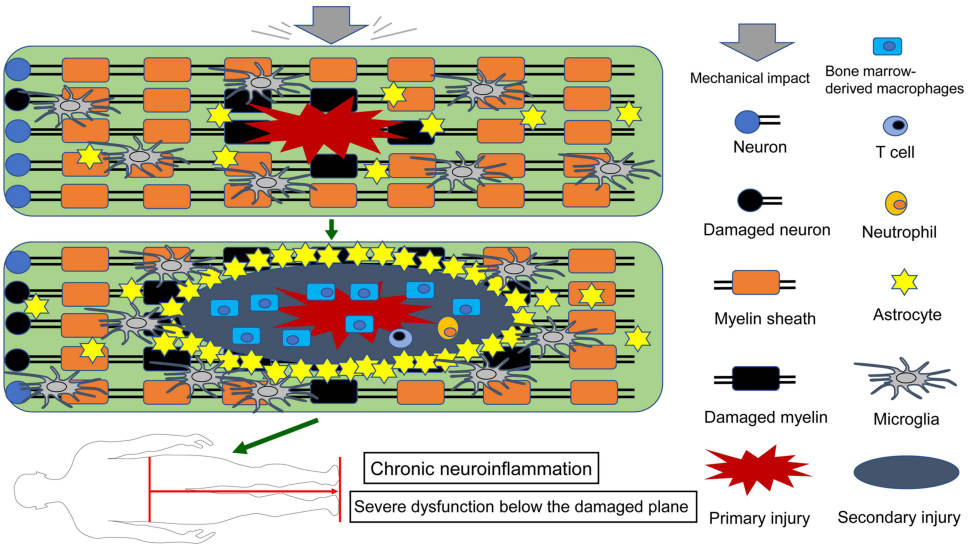

Figure 1 Schematic depicting the activation and migration of resident and peripheral immune cells following SCI. After primary injury, resident astrocytes, microglia, and other glial cells are immediately activated and migrate to the injury site (top). Subsequently, peripheral inflammatory cells including neutrophils, bone marrow-derived macrophages, and lymphocytes infiltrate into the epicenter of the injured spinal cord, and these activated immune cells can exacerbate damage, causing a wider range of secondary injury. Glial cells (mainly astrocytes) form glial scar to seclude the damaged area, and microglia are mainly present around the injury site (middle). These persistent pathophysiological changes ultimately result in severe dysfunction below the damaged segment (bottom).

main types of immune cells together with their secretion of various neurotoxic factors including inflammatory mediators, free radicals, matrix metalloproteinases, proteolytic enzymes, ROS, and apoptosis-inducing molecules extend the primary damage to adjacent normal tissues, causing further apoptosis and necrosis of neurons and glial cells.[48,49]

During the course of skin and muscle wound healing, there is generally a distinct shift in the inflammatory response. Initially, various pro-inflammatory cells such as M1 macrophages and neutrophils predominate the lesion site.[50] They play critical roles in removing cell debris and providing a sterile microenvironment for tissue regeneration.[51] Following beneficial and transient inflammation, an anti-inflammatory and reparative phase is induced that is mainly regulated by regulatory T cells (Treg) and M2 macrophages, which can promote angiogenesis and extracellular matrix deposition.[52,53] However, unlike the cutaneous and muscular healing processes, there is no corresponding anti-inflammatory and remodeling phase after SCI.[54] Pro-inflammatory cells persist at the lesion site, resulting in secondary neuronal and glial degeneration, which further exacerbates neurological dysfunction.[55] Effective strategies to induce the anti-inflammatory remodeling phase after the acute inflammatory response are extremely important for promoting neurological recovery post-SCI.

Contribution of Distinct Immune Cells to SCI Inflammation

The inflammatory response plays critical roles in all the mechanisms of secondary injury and directly influences the neurological outcome post-injury.[56] Neuroinflammation was previously regarded as an adverse consequence after SCI because it led to a broader range of destructive processes including widespread healthy spinal cord tissue damage and further neuronal degeneration. With substantial advances in the understanding of SCI pathophysiology, it was gradually revealed that the early inflammatory response could also generate a permissive microenvironment for the regeneration of damaged neurons and axons, similar to early inflammatory benefits in other tissues.[57–59] Neuroinflammation is composed of multifaceted cellular and molecular responses, and the unique effects of immune cells including macrophages, astrocytes, and lymphocytes are essential for the occurrence and progression of inflammatory responses post-SCI.[60]

Effect of Macrophages on Neuroinflammation

The phase-specific functions of macrophages—ranging from initial neuroinflammation to eventual tissue remodeling and repair—are essential for functional locomotion recovery.[55] These cells primarily originate from resident microglia that

are activated minutes to hours after SCI, but after 2 days they are mainly from circulating monocytes.[61] These monocyte- and microglia-derived macrophages are still hard to distinguish owing to their similar phenotypes and morphologies.[60,62] Based on their phenotypic and functional differences, macrophages can be divided into two main subtypes termed M1 and M2.[63] T-helper 1 (Th-1) cytokines such as TNF-α and interferon gamma (IFN-γ) induce the polarization of classically activated M1 macrophages characterized by up-regulation of inflammatory cytokines such as IL-23, IL-1β, TNF-α, and IL-12.[64,65] These mediators can kill neurons, induce axonal degeneration, and further contribute to the activation of neurotoxic Th1 and Th17 cells.[66,67] In contrast, alternatively activated M2 macrophages are the product of exposure to Th2-associated cytokines such as IL-4 and IL-13.[68,69] These cells are able to produce high levels of anti-inflammatory cytokines such as IL-10, IL-4, and TGF-β, which are essential for inhibiting excessive inflammatory responses and promoting wound remodeling and repair.[69,70] In rat models of SCI, M2 macrophages can be observed early, but dissipate rapidly within 3–7 days after injury, while M1 macrophages remain in the lesion indefinitely.[31,71] In SCI patients, by ~5 days post-injury, activated macrophages are abundant in the spinal cord for up to a year, and these cells could produce potentially destructive oxidative and proteolytic enzymes.[45]

Effect of Astrocytes on Neuroinflammation

It was previously believed that macrophages were the only cell type involved in neuroinflammation. However, it is now known that astrocytes are able to modulate innate and adaptive immune responses in the CNS by activating diverse pathways.[38,72,73] For example, as a critical modulator for neuroinflammation, nuclear factor (NF)-κB signaling is highly activated by its associated gene expression after SCI, suggesting that this pathway is important in the pathophysiological process of CNS injury.[74–76] In a mice model of SCI, inhibiting astroglia NF-κB was demonstrated to down-regulate monocyte chemoattractant protein (MCP)-1 expression, inhibit leukocyte recruitment, and promote axonal regeneration and germination, finally facilitating functional locomotion recovery.[77–79] Furthermore, inhibiting the activation of astrocytes after SCI has been shown to attenuate inflammation and promote axonal regeneration and motor recovery.[80] Paradoxically, Anderson et al[81] demonstrated that attenuating scar-forming astrocytes elicited a more severe inflammatory response and prevented axonal regeneration in the CNS, leading to more severe dysfunction. These diverse outcomes are likely to be explained by the induction of an astrocyte reaction that is both phenotypically and functionally heterogeneous. Similar to the situation of M1 and M2 macrophages, study has revealed that astrocytes have more than one type of polarization.[44] Inflammation and ischemia induce the pro-inflammatory A1 and anti-inflammatory A2 phenotypes.[82] It should be noted that the current nomenclature oversimplifies the astrocyte activation continuum, implying that reactive astrocytes have more than two polarization types. The naming convention of A1/A2 is intended to promote scientific research and academic exchanges.[83,84] A1 astrocytes strongly increase the expression of the classical complement cascade genes including complement component1s (C1s), C1r, C3, and C4, which were previously shown to be harmful to synapses, indicating that A1 astrocytes might be the "bad" player in neurological repair and remodeling.[85,86] In contrast, A2 astrocytes up-regulate the expression of neurotrophic factors and cytokines such as leukemia inhibitory factor, cardiotrophin-like cytokine factor 1, IL-10, and IL-6 to support neuronal restoration and survival, as well as synaptic repair, suggesting that A2 astrocytes might be the "good" players in neuroinflammation.[87–89] Therefore, differentiation of astrocytes into an A2 phenotype may facilitate functional recovery after SCI while inhibiting secondary inflammation-mediated damage. These researches have emphasized the phenotypic and functional heterogeneity of reactive astrocytes. However, current studies mainly focus on the rodent astrocytes that have been shown to be significantly different from human astrocytes in morphology, activation timing, and gene expression.[90] Hence, it is unclear whether the gene expression and regulation of reactive astrocyte subtypes observed in rodents are directly applicable to human tissues.[90] But researchers can explore more extensively by selecting suitable model species, such as non-human primates, whose astrocytes have a transcription profile similar to that of human astrocytes.

Effect of T Lymphocytes on Neuroinflammation

T lymphocytes play important roles in the pathogenesis of neuroinflammation following CNS injury.[91] As a key modulator of the adaptive immune response, CD4+ T cells mainly differentiate into four subtypes—Th1, Th2, Th17, and Treg cells—that are essential for affecting the outcome of inflammatory response by restricting or activating other

immune cell responses.[92,93] Each CD4+ T cell subtype has a specific transcriptional program and cytokine expression pattern that can aggravate or mitigate the degree of secondary injury.[94] CNS injury recovery is likely to depend on the balance among these subtypes.[95] Th1 cells are the product of exposure to IFN-γ and IL-12 and can induce activation of the Th1-associated specific transcription factor, T-bet, which feeds back to stimulate the expression of additional IFN-γ, IL-12, and TNF-β, thereby promoting macrophage-dependent neuroinflammation and cell-mediated immunity.[66,96,97] T-bet-mediated cytokines are also able to induce Th2 phenotype repolarization toward Th1.[98] Hence, Th1 might play destructive roles in CNS injury and repair. The key cytokine required for Th2 differentiation is IL-4, which contributes to the expression of the master regulator transcription factor GATA3 of Th2, and itself is released by Th2 in addition to IL-13 and IL-10.[99,100] Known effector functions of Th2 include promoting eosinophil accumulation and inducing B cells to produce immunoglobulin (Ig)E and IgG1, as well as inhibiting M1 macrophage activation.[66] Some studies have demonstrated that shifting CD4+ T cells to Th2 by potent Th2 inducers like glatiramer acetate can improve the outcome of CNS injury.[101] As such, Th2 cells have a greatly protective role. Apart from Th1 and Th2 cells involved in the neuroinflammation, study has shown that both Th17 cells and Treg are essential to regulate the immune response post-SCI.[91] Th17 cells are defined by the characteristic production of IL-17A, IL-17F, IL-21, and IL-22 along with the expression of the master transcription factor RORγt.[102] Th17 cells are pro-inflammatory and essential to protect against pathogens by recruitment of neutrophil granulocytes.[103] This cell type plays a determinant role in various inflammatory diseases, including multiple sclerosis, ankylosing spondylitis, inflammatory bowel disease, and rheumatoid arthritis, as well as SCI.[104,105] In contrast, Treg are characterized by the specific transcription factor Foxp3 and play a significant role in inhibiting immune response-related neuroinflammation by secreting anti-inflammatory cytokines such as TGF-β and IL-10.[106,107] Th1 and Th17 cells are considered to be the main drivers of pathogenesis because they predominate at the lesion site where they further induce an inflammatory response by activating macrophages and neutrocytes.[108] Accumulating data suggest that correcting the imbalance of Th1/Th2 and Th17/Treg cells could improve the prognosis of SCI.

Contribution of MSCs Transplantation to SCI Prognosis

A premise of effective MSC-based therapy is that MSCs migrate from their sources via the bloodstream and home to the injured site.[118,119] Researchers have revealed that MSCs are attracted to the area of damage by various diverse chemokines, such as platelet-derived growth factor-AB, stromal-derived factor-1, and macrophage-derived chemokine.[120] Study has uncovered that MSCs express a large amount of CXCR4, which is essential for their homing and migrating.[121] However, natural migration into lesion sites is extremely limited.[122] A similar situation is observed to be found when MSCs are systemically administered because they are trapped in vascularized tissues, especially the lungs.[119] Therefore, an effective and simple MSCs transplantation method is local injection into the damaged area or surrounding healthy tissue.[123] Initial attention mainly focused on the differentiation potential of MSCs because they might differentiate into neurons and glial cells to replace the dead cells and reconstruct the integrity of neuronal conductive pathways; however, there remains a lack of related differentiation evidence.[112,117] Interestingly, MSCs engraftment can still improve various functional parameters in animal models of SCI[124] (Table 1). Scientists proposed that these results might be largely explained by their paracrine effects or direct interactions with immune cells.[125]

Angiogenesis is particularly important for the recovery of neurological function, so it is a valuable research direction for wound healing processes.[33] Studies have shown that MSCs significantly promote angiogenesis by secreting a series of factors, including vascular endothelial growth factor, platelet-derived growth factor, TGF-β, and IL-6, which promote BSCB repair and neurogenesis after SCI.[126–128] Meanwhile, an increasing body of evidence shows that MSCs transplanted into SCI models release many neurotrophic factors such as glial cell-derived neurotrophic factor, BDNF, neurotrophin-3, and basic fibroblast growth factor; the production of these soluble factors contributes to the inhibition of cell apoptosis and necrosis and regeneration of axons and myelin sheaths.[129–131] Apart from these reparative properties, MSCs also have robust anti-inflammatory roles.[130,132] For example, bone marrow-derived mesenchymal stem cells (BM-MSCs) transplanted into a rat model of SCI can reduce the infiltration of neutrophil and significantly down-regulate the expression of pro-inflammatory cytokines.[133] In addition to neutrophil, MSCs can also skew the balance of inflammatory cytokines in an anti-inflammatory direction by modulating the state of macrophages, astrocytes, and T

Table 1 The Immunomodulatory Mechanisms of Transplanted MSCs in Improving the Prognosis of SCI

Species of MSCs	Source	Model	Dose (Number)	Injection Site	Infusion Time	Effect	Molecular Mechanism	Refs.
Mice	Adipose	Mice	1.0× 10^6	Intralesional	The day after SCI	Promote functional recovery	Inhibit the infiltration of macrophages and reduce the expression of TNF-α, IL-1β and IL-6	[109]
Human	Bone marrow	Rat	N/A	Intralesional	7 days after SCI	Promote functional recovery	Reduce TNF-α, IL-1β, IL-2, IL-6 and IL-12, increase the levels of MIP-1α	[110]
Human	Bone marrow	Mice	5.0×10^5	Intralesional	The day following SCI	Improve locomotor activity and suppress SCI-related damage	Up-regulate the levels of TSG-6, IL-10, TGF-β and IL-4, induce an AAM environment	[111]
Human	Bone marrow	Rat	1.0× 10^6	Intralesional	3 days after SCI	Promote functional recovery	Activate M2 macrophages, inhibit M1 macrophages, up-regulate the levels of IL-4 and IL-13, down-regulate the levels of TNF-a and IL-6	[112]
Rat	Bone marrow	Rat	1.0×10^6	Intravenous	24 hours after SCI	Promote functional recovery	Suppress the expression of pro-inflammatory cytokines such as TNF-α and IL-1β	[113]
Human	Umbilical cord	Mice	1.0× 10^6	Intralesional	14 days after SCI	Promote functional recovery	Promote the polarization of M2 macrophages, reduce the expression of IL-7, IFN-γ, and TNF-α, increase the expression levels of IL-4 and IL-13	[114]
Human	Umbilical cord	Mice	1.0×10^5	Intralesional	1 day after SCI	Improve locomotor performance	Shift the macrophage phenotype to the M2 phenotype	[115]
Human	Deciduous teeth	Rat	6.0×10^5	Intralesional	The day after SCI	Promote functional recovery	MCP-1 and ED-Siglec-9 secreted by MSCs synergistically induce M2 macrophages, suppress proinflammatory mediators such as IL-1 and TNF-a	[116]
Rat	Peripheral blood	Rat	2.0×10^4	Intralesional	30 minutes after SCI	Promote functional recovery	Inhibit Th17 cells, activate Treg cells, down-regulate the levels of IL-6 and IL-17a	[117]

Abbreviations: MIP-1α, macrophage inflammatory protein-1α; AAM, alternatively activated M2; N/A, not applicable.

cells.[130] Harnessing the ability of MSCs to regulate neuroinflammation might be a powerful tool to inhibit secondary injury, which is potentially good news for SCI patients (Table 2).

MSCs for SCI: Macrophage-Mediated Neuroinflammation

Macrophages are the most common immune cells at the lesion site and exert key roles in mediating the neuroinflammation during distinct periods post-SCI. Polarized macrophages can help facilitate angiogenesis and modulate connective tissue synthesis, which are the crucial elements of the damaged spinal cord repair, but can also cause deterioration of extracellular matrix and damage neurons and glia.[134] The change of macrophages from a pro-inflammatory to an anti-inflammatory, remodeling phenotype is considered to support the recovery of nerve function and the integrity of the injured tissue.[31] Numerous studies have reported that macrophages co-cultured with MSCs have a cytokine secretion pattern similar to M2 macrophages, which are characterized by the up-regulation of IL-4 and IL-10 along with down-regulation of TNF-α, IL-1β, and IL-12.[135–138] A similar situation can also be observed in M0 macrophages co-cultured with MSC-conditioned medium (MSC-CM), indicating that soluble factors are essential for their immunomodulatory properties.[139] These previous studies in vitro have raised our attentions about the polarization of macrophage in MSCs engraftment following SCI. Nakajima et al[112] reported that after MSCs transplantation in the injured spinal cord, M2 macrophages and their associated cytokines IL-13 and IL-4 were significantly increased, while M1 macrophages and their associated cytokines TNF-α and IL-6 were significantly decreased, resulting in axonal regeneration, inhibition of glial scar formation, and increased myelin sparing. Subsequently, it was shown in rat models of SCI that exosome (exo) derived from adipose-derived MSCs could also shift the macrophage phenotype from M1 to M2, accompanied by down-regulation of the pro-inflammatory cytokines IFN-γ and TNF-α, and this promoted a pro-regenerative environment.[140] To date, the accumulated evidence confirms that MSCs can skew the balance between M1/M2 macrophages towards the M2 phenotype, thereby facilitating functional neurological improvement post-SCI.[141,142]

Study investigating the mechanism involved found that this effect was associated with some soluble factors secreted by MSCs.[134] Stimulated MSCs can significantly secrete numerous cytokines including TGF-β, indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), IL-4, and IL-6 following stimulation by inflammatory mediators. These diverse soluble factors play an essential role in shifting the macrophage phenotype from M1 to M2.[134,143–150] Notably, we previously showed that inflammatory macrophages could activate the NF-κB pathway of peripheral blood-derived mesenchymal stem cells (PB-MSCs) by releasing TNF-α and IL-1β, resulting in the up-regulation of IL1-RA of PB-MSCs, which could induce the macrophage polarization towards M2 phenotype.[151] In response to inflammatory stimuli, MSCs up-regulated the expression levels of tumor necrosis factor-induced protein 6, which could reduce the nuclear translocation of NF-κB by binding to the resident macrophages' CD44 receptor, thereby weakening the macrophages-mediated inflammatory cascade.[143,152] Moreover, IL-10 secreted by MSCs is likely to shift the macrophage phenotype towards anti-inflammatory M2 by activating Janus kinase (JAK)/signal transducer and activator of transcription (STAT)3 signaling.[153–155]

In summary, MSCs have emerged as promising immune-modulators of macrophages polarization by modulating the production of distinct cytokines. Identifying the regulatory factors and key pathways of MSCs-mediated macrophage polarization is the key to shifting the macrophage phenotype from M1 to M2, thus creating an anti-inflammatory microenvironment for axonal extension and functional recovery. However, the specific effects of different subtypes on functional recovery should be fully considered when designing macrophage polarization as an immunomodulatory strategy.

MSCs for SCI: Astrocyte-Mediated Neuroinflammation

Astrocytes are the most abundant glial cells in the CNS, and they are essential for the homeostasis of the CNS.[156] As mentioned above, reactive astrocytes are highly heterogeneous after SCI and have been identified in two distinct categories, A1 and A2. Liddelow et al[157] have reported that classically activated neuroinflammatory microglia shift astrocytes to the A1 phenotype by releasing TNF-α, IL-1α, and C1q, which together are sufficient and necessary. A1 astrocytes lose most of their original functions and show new features, including rapidly killing the neurons and mature differentiated oligodendrocytes.[158] Therefore, efforts should be focused on inhibiting the activation of A1 astrocytes for

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Table 2 Completed Clinical Trials of MSCs in the Treatment of SCI

Clinical Trials. Gov Identifier	Status	Phase(s) (No. Enrolled)	Completion Date	Primary End Point	Ages (Years)	Intervention	Transplantation	Findings
NCT02482194	Completed	I (N=9)	Mar 2016	Safety	18~50	Autologous BM-MSCs	Intrathecal	Intrathecal injection of BMMSCs is safe with no serious adverse event
NCT01676441	Terminated	II/III (N=20)	Mar 2021	Safety, ASIA score	16~65	Autologous BM-MSCs	Intrathecal	Patients receiving BM-MSCs demonstrate improved in the muscle tension and in ADL, as well as significant MRI and electrophysiological changes
NCT02481440	Completed	I/II (N=102)	Mar 2020	Safety, ASIA score	18~65	Allogeneic hUC-MSCs	Intrathecal	Intrathecal injection of hUC-MSCs is safe with no serious adverse event
NCT02152657	Completed	N/A (N=5)	Dec 2016	Safety, MRI	18~65	Autologous MSCs	Percutaneous	N/A
NCT02981576	Completed	I/II (N=14)	Jan 2019	Safety and efficacy, ASIA score, MRI	18~70	Autologous BM-MSCs and AD-MSCs	Intrathecal	N/A
NCT02570932	Completed	II (N=10)	Dec 2017	IANR-SCIFRS	18~70	Autologous BM-MSCs	Intrathecal	Patients receiving BM-MSCs show variable clinical improvement in sensitivity, motor power, spasms, spasticity, neuropathic pain, sexual function or sphincter dysfunction without any adverse event
NCT01769872	Completed	I/II (N=15)	Jan 2016	Safety and effect, ASIA score	19~70	Autologous AD-MSCs	Intrathecal	N/A
NCT01274975	Completed	I (N=8)	Feb 2010	Safety	19~60	Autologous AD-MSCs	Intravenous	N/A
NCT01624779	Completed	I (N=15)	May 2014	MRI	19~70	Autologous AD-MSCs	Intrathecal	N/A
NCT04288934	Completed	I (N=20)	Sep 2020	ASIA score, ISNCSCI, SCIM III	18~70	Autologous BM-MSCs, WJ-MSCs	Intralesional.	N/A
NCT01873547	Completed	III (N=300)	Dec 2015	Safety, ASIA score	20~65	Allogeneic UC-MSCs	Intrathecal	N/A
NCT01909154	Completed	I (N=12)	Mar 2015	Safety	18~60	Autologous BM-MSCs	Intrathecal	Intrathecal administration of BM-MSCs is safe with no adverse events
NCT00816803	Completed	I/II (N=80)	Dec 2008	Safety, MRI	10~36	Autologous BM-MSCs	Intrathecal	Intrathecal injection of BM-MSC is safe with no long-term cell therapy-related side effects

NCT02165904	Completed	I (N=10)	May 2016	ASIA score	18~70	Autologous BM-MSCs	Intrathecal	Patients treated with BM-MSCs show improvements in sensitivity, motor function, sexual function and urinary control
NCT02510365	Unknown	I (N=20)	Dec 2021	Safety and efficacy	18~65	Allogeneic UC-MSCs	Intralesional	UC-MSCs transplantation is safe with no obvious adverse symptoms
NCT01393977	Unknown	II (N=60)	May 2012	EET	20~50	Allogeneic UC-MSCs	Intrathecal	Patients receiving UC-MSCs demonstrate improved self-care ability, muscular tension, maximum urinary flow rate as well as maximum bladder capacity
NCT01162915	Suspended	I (N=10)	May 2014	Safety	18~65	Autologous BM-MSCs.	Intrathecal	N/A
NCT01325103	Completed	N/A (N=14)	Dec 2012	Safety	18~50	Autologous BM-MSCs	Intralesional	Patients treated with BM-MSCs show improvement in both urinary and nervous system function and AISA score
NCT03003364	Completed	I/II (N=10)	Feb 2020	Safety	18~ 65	Allogeneic WJ-MSCs	Intrathecal	Intrathecal transplantation of WJ-MSCs is safe with no significant side effects
NCT01694927	Unknown	II (N=30)	Jun 2014	Safety	2~65	Autologous MSCs	Intrathecal	N/A
NCT02574572	Unknown	I (N=10)	Jun 2020	MRI	18~65	Autologous MSCs	Intralesional	N/A
NCT01446640	Unknown	I/II (N=20)	Jun 2014	Safety	16~60	Autologous BM-MSCs	Intrathecal	N/A
NCT02688049	Unknown	I/II (N=30)	Dec 2021	ASIA score, SSEP, MEP	18~65	Autologous BM-MSCs	Intralesional	N/A
NCT02352077	Unknown	I (N=30)	Dec 2021	Safety	18~65	Autologous BM-MSCs	Intralesional	N/A
NCT05018793	Suspended	I (N=15)	Dec 2025	Safety	Child, adult, older	Autologous AD-MSCs	Intrathecal	Intrathecal administration of AD-MSCs is safe with no adverse events
NCT04213131	Unknown	N/A (N=42)	Jan 2021	Neurologic function score, ASIA score	20~65	Allogeneic hUC-MSCs	Intravenous	N/A

Abbreviations: ASIA, American spinal injury association; ISNCSCI, international standards for neurological classification of SCI; MEP, motor evoked potentials; SSEP, somatosensory evoked potentials; MRI, magnetic resonance imaging; SCIM, spinal cord independence measure; IANR-SCIFRS, neurorestoratology-spinal cord injury functional rating scale; N/A, not applicable; EET, electromyogram and electroneurophysiologic test; hUC-MSCs, human umbilical cord-derived mesenchymal stem cells; UC-MSCs, umbilical cord derived mesenchymal stem cells; AD-MSCs, adipose tissue-derived mesenchymal stem cells; WJ-MSCs, wharton's jelly mesenchymal stem cells.

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the treatment of SCI. In response to lipopolysaccharide (LPS), A1-related cytokine, IL-1β and TNF-α, is significantly up-regulated, but this is inhibited when astrocytes are pre-treated with MSC-CM.[159] Recently, study has shown that BMMSC-exo transplanted into contusive SCI rat models could significantly reduce the number of A1 neurotoxic astrocytes by inhibiting the activation of inflammatory macrophages, thereby effectively promoting angiogenesis and axonal regeneration, and reducing neuronal apoptosis and inflammatory response. Furthermore, Wang et al found that BM-MSCs and BMMSC-exo could both directly hinder astrocytes from polarizing toward the pro-inflammatory A1 phenotype after SCI by inhibiting the nuclear translocation of NF-κb p65, thereby reducing the lesion area and levels of IL-1β, TNF-α, and IL-1α, as well as increasing the expression of myelin basic protein, marker of neuronal nuclei, and synaptophysin.[160,161] These results suggest that MSCs and MSC-exo can not only directly inhibit the formation of A1 astrocytes after SCI, but also indirectly suppress the polarization of A1 astrocytes by preventing the activation of inflammatory macrophages.

JAK/STAT3 pathway activation is critical for astrocyte proliferation, polarization, and growth.[84,89,162] After CNS injury, IL-6 secreted by transplanted MSCs might mediate the polarization of A2 astrocytes by activating JAK/STAT3 signaling, thus significantly improving the neurological recovery.[163] Besides, in models of systemic LPS activation, IL-10 secreted by M2 macrophages can induce astrocytes polarization toward the anti-inflammatory A2 phenotype, accompanied by significant up-regulation of TGF-β, which could also greatly shift the macrophage phenotype towards M2, with lower expression of IL-6 and IL-1β and high levels of CX3CR1 and IL-4Rα. Hence, the interaction between M2 macrophages and A2 astrocytes is beneficial to generate an anti-inflammatory and reparative microenvironment.[164] As mentioned above, MSCs and MSC-exo can drive macrophage toward an M2 phenotype. Taken together, it is possible that MSCs and MSC-exo exert effects on A2 astrocytes not only in a direct way but also mediated through the activation of M2 macrophages, thereby exerting a powerful immunosuppressive function and breaking the inflammatory cascade reaction after SCI. Other studies have revealed that in response to TGF-β, PI3K/AKT signaling in astrocytes modulates various physiological events, such as activation, proliferation, growth, and survival. PI3K/AKT pathway activation also induces astrocyte polarization toward the A2 phenotype; it is well known that MSCs can constitutively produce TGF-β.[165–169] Taken together, the evidence suggests that TGF-β secreted by MSCs may mediate astrocyte polarization in the A2 phenotype through the PI3K/AKT pathway. However, more specific studies are needed to clarify this issue.

MSCs for SCI: T Lymphocyte-Mediated Neuroinflammation

The excessive inflammatory Th1 and Th17 phenotypes observed following SCI tilt the scale toward the pro-inflammatory environment, which exacerbates the damage to neural tissue within weeks or even months.[49] We have recently demonstrated that after direct culture of CD4+ T cells and PB-MSCs in vitro, the Th17/Treg ratio and levels of pro-inflammatory cytokines IL-17 and IL-6 were significantly down-regulated, while the levels of anti-inflammatory cytokines TGF-β, IL-10 and Foxp3 were significantly up-regulated.[135] Moreover, BM-MSCs could also suppress the proliferation, activation, and differentiation of Th17 and Th1 cells and induce Treg polarization in vitro.[170] After interacting with dendritic cells, MSCs shift from the Th1 to Th2 subtype, and this is accompanied by higher levels of anti-inflammatory cytokines.[171] MSC-exo is also reported inhibiting T cell proliferation and activation and shift their phenotype towards the anti-inflammatory Treg, with a corresponding beneficial change in the cytokine profile.[92,172,173] Altogether, these results suggest that MSCs can inhibit Th1 and Th17 cell differentiation and induce Th 2 and Treg cells in vitro. Notably, our team has found that PB-MSCs transplanted into rat models of SCI caused decreases in CD4 + IL17 + Th17 cells along with their associated cytokines IL-6 and IL-21, and increases in the numbers of CD4 + CD25 + Foxp3 + Treg cells and their associated cytokines Foxp3, TGF-β, and IL-10; these changes ultimately contributed to improved functional recovery.[117] Furthermore, various activated CD4+ T cell subtypes can form a complex network regulatory system by coordinating and antagonizing other immune cell types. For example, Th1 cells can induce the differentiation of macrophages into M1 phenotype, while Th2 cells can induce the polarization of M2 macrophages that are involved in the induction of Treg. Therefore, in addition to directly regulating each immune cell, the application of MSCs may provide an anti-inflammatory and stable environment for nerve tissue repair by breaking this inflammatory cascade reaction.

Further investigations reveal that MSCs stimulated by IFN-γ can significantly up-regulate IDO expression levels; this results in tryptophan degradation that inhibits the allogeneic T cell response, promotes Th2 to secrete IL-4, and prevents Th1 from producing IFN-γ.[171,174] MSCs are also able to suppress T cell proliferation and the secretion of related inflammatory cytokines by producing nitric oxide and PGE2, and PGE2 can also prevent CD4+ T cells from differentiating into Th17 cells.[175–178] Moreover, studies have demonstrated that MSCs can exert their inhibitory effects on CD4+ T cell differentiation towards Th1 and Th17, possibly due to induction of Treg and IL-10 secretion.[170,179] Furthermore, MSC-mediated Treg induction can be inhibited by a TGF-β blocker, indicating that TGF-β secreted by MSCs plays a critical role in the differentiation of CD4+ T cells into Treg.[180,181] Despite the fact that soluble factors are involved in Treg induction, ICOSL (inducible T cell costimulatory ligand) expression in MSCs is also essential for contact-dependent modulation of MSC-mediated Treg polarization.[182] These results suggest that MSC-mediated CD4+ T cells polarization may be modulated by different mechanisms depending both on soluble factors and cell-surface proteins.

In conclusion, the immunomodulatory role of MSCs in CNS injury involves multiple immune cell types. These immune cells can modulate MSCs gene expression, which subsequently inhibits the immune response of these innate and adaptive immune cells to produce an immunotolerant and permissive micro-environment (Figure 2). All the achievements in MSCs engraftment bring hope to the successful transformation, but in vivo models of SCI currently used by researchers are mainly small rodents, such as rats and mice. Although this animal model is cost-effective and easy to feed, it is necessary to use larger animal models, such as non-human primates to further confirm the safety and efficacy of MSCs in improving nerve regeneration after nerve injury because their size and neuroanatomical structure are similar to those of human specimens.[183] Furthermore, in order to enhance the therapeutic effect of MSCs, more research is needed in the future to determine the ideal number of cells for transplantation, cell source, timing of administration, and route of administration.

Prospective

Although transplanted MSCs are able to improve anatomical and locomotor recovery after SCI, the post-injury inflammatory and toxic environment is not suitable for the survival of grafted cells.[195,196] Therefore, any strategy that enhances the viability and proliferation of transplanted MSCs is of great value.[197,198] It is noteworthy that preconditioning can effectively enhance the immunomodulatory and survival ability of MSCs in vitro and in vivo (Figure 3)[127] (Table 3). For example, MSCs pretreated with cobalt chloride could improve their homing ability by up-regulating levels of hypoxia-inducible factor-1α and CXCR4; simultaneously they can decrease their apoptosis rate by down-regulating caspase-3 and Bcl-2 levels. These hypoxic MSCs can also significantly inhibit macrophage polarization toward the pro-inflammatory M1 phenotype, along with lower levels of pro-inflammatory cytokines TNF-α and IL-1β.[186] Furthermore, MSC-exo harvested from hypoxic MSCs could significantly shift the macrophage phenotype from M1 to M2 by

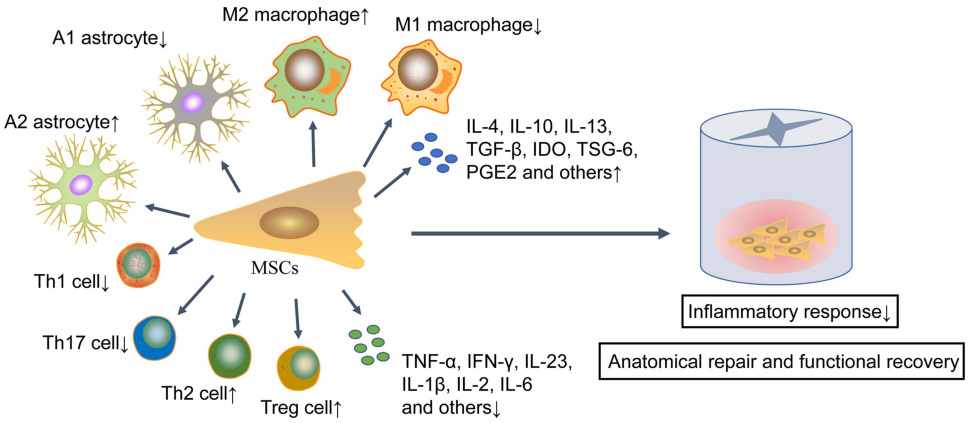

Figure 2 MSCs improve SCI prognosis via immunomodulatory effects. These transplanted MSCs inhibit an excessive inflammatory response by up-regulating anti-inflammatory immune cells and associated cytokines and down-regulating the pro-inflammatory immune cells and associated cytokines, thereby promoting anatomical repair and functional recovery.
Notes: ↑, promotion; ↓, inhibition.

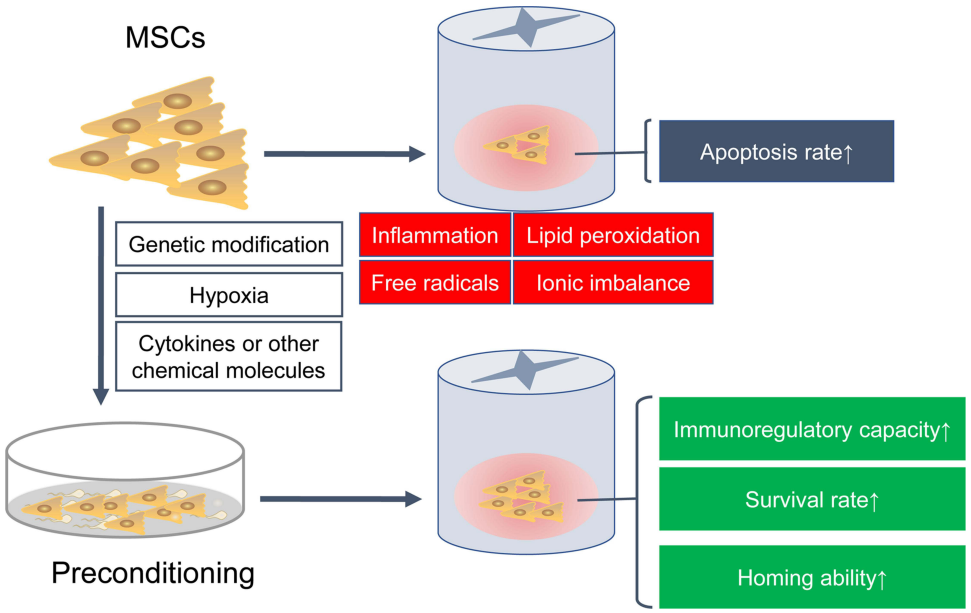

Figure 3 Preconditioning enhances the immunomodulatory ability and survival rate of MSCs in SCI. After SCI, the local harsh microenvironment causes a large amount of transplanted MSCs apoptosis. Various preconditioning strategies, including genetic modification, cytokines, hypoxia or other chemical molecules, can improve the immunomodulatory capacity, survival rate and homing ability of transplanted MSCs.
Note: ↑, promotion.

modulating the TLR4/NF-κB/PI3K/Akt pathway, thereby promoting functional and behavioral recovery.[188] Furthermore, moringin-pretreated MSCs significantly down-regulated COX-2 and IL-1β levels in the spinal cord and reduced cellular apoptosis by decreasing the expression levels of Bax, caspase-3, and caspase-9 and increasing levels of the anti-apoptotic protein Bcl-2.[185] In another study, it was revealed that the treatment of MSCs with IL-1β and IFN-γ enhanced their ability to induce macrophage polarization towards an anti-inflammatory M2 phenotype in comparison to MSCs treated with nothing.[199] These results indicate that hypoxia or cytokine preconditioning has a strong cytoprotective effect, which can help them adapt to the new environment during the acute phase of transplantation.

Gene modification might serve as another unique way to further improve MSCs immunomodulatory capacity. IL-35 is necessary for Treg to exert the maximum regulatory activity in vivo and in vitro.[200,201] MSCs over-expressing IL-35 could significantly increase the percentage of CD4 + CD25 + Treg and suppress the effects of Th1 and Th17 cells. One study showed that compared with an untreated MSCs group, expression of the pro-inflammatory cytokine IL-17A was significantly down-regulated, while IL-10 was significantly up-regulated in the IL-35-transduced MSCs group.[201] Additionally, MSCs over-expressing IL-13 could significantly shift the macrophage phenotype to anti-inflammatory M2, thereby promoting the functional and histopathological recovery of SCI mouse models.[202] Although genetic modification of MSCs can promote cell survival and immunomodulatory capacity, safety concerns are the main limitations for the future therapeutic application of genetically modified MSCs, as viral vector integration may cause tumorigenesis in recipients after long-term treatment.

Taken together, the inflammatory cascade is a major contributor to secondary damage and directly affects disease progression. Macrophages, astrocytes, and T cells are the major cell types involved in SCI neuroinflammation, but no existing therapy directly targets neuroinflammation. Over the past few decades, MSCs have emerged as attractive, transplantable, and reparative cells that can not only directly modulate the activation of macrophages, astrocyte, and T cells, but also can break their complex inflammatory cascade reaction, thereby providing an anti-inflammatory and permissive microenvironment for CNS regeneration and repair. Considering that a pro-inflammatory and toxic micro-environment has harmful effects on the survival and immunoregulatory capacity of transplanted MSCs, pretreatment may enhance the ability of MSCs and further improve the ability to inhibit robust inflammation. However, further researches

Table 3 The Immunosuppressive Effect of Pretreated MSCs and Extracellular Vesicles Secreted by MSCs in SCI

Source	Pretreatment	Dose (Number)	Model	Way	Infusion time	Secretion of MSCs	Immunomodulatory Mechanism	Effect	Refs.
Human umbilical cord	Hypoxia	1×10^5	Rat	Intralesional	N/A	N/A	Up-regulate the levels of regenerative neurotrophic factors, inhibit microglial/ macrophage infiltration	Promote functional recovery	[184]
Human gingiva	Vesicular moringin nanostructures	1×10^6	Mice	Intravenous	1h hour after SCI	N/A	Increase the levels of anti-inflammatory cytokines such as IL-10 and TGF-β	Promote functional recovery	[185]
Rat bone marrow	Hypoxia	1×10^6	Rat	Intralesional	The day following SCI	N/A	Down-regulate the levels of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6	Improve motor and sensory function	[186]
Human umbilical cord	N/A	1, 2, 3ug	Rat	Intrathecal	24 h after SCI	EVs	Decrease the expression of caspase-1, IL-1, IL-18 and TNF-α	Improve locomotor function	[187]
Human umbilical cord	N/A	25μg	Mice	Intravenous	1 h and 7 days after SCI	N-NVs	N-NVs shift the balance from M1 to M2 macrophages	Promote functional recovery	[142]
Rat bone marrow	Hypoxia	200μg	Mice	Intravenous	The day following SCI	Exosome	Promote microglia/macrophage polarization from M1 to M2 phenotype, inhibit the TLR4 pathway	Promote functional recovery	[188]
Rat bone marrow	N/A	2.5×10^9	Rat	Intravenous	1 week after SCI	Exosome	Increase the production of anti-inflammatory cytokines, block M2 macrophages from converting to an M1 pro-inflammatory activation state	N/A	[189]
Rat bone marrow	N/A	N/A	Rat	Intravenous	7 consecutive days after SCI	Exosome	Increase the expression levels of anti-inflammatory factors such as IL-10 and IL-4, decrease the levels of TNF-a, IL-1b and MCP-1	Promote functional recovery	[190]
Human umbilical cord	Overexpression of NT-3	1×10^6	Rat	Intralesional	1 week after SCI	NT-3	Reduce the accumulation of immunoreactive macrophages/microglia	Promote functional recovery	[191,192]
Mice bone marrow	Overexpression of IGF-1	1×10^6	Mice	Intralesional	N/A	IGF-1	Up-regulate antioxidant defense genes and the expression levels of Mrc1, Nfe2L2, reduce the levels of MDA, nitrite	Promote functional recovery	[193]

(*Continued*)

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Table 3 (Continued).

Source	Pretreatment	Dose (Number)	Model	Way	Infusion time	Secretion of MSCs	Immunomodulatory Mechanism	Effect	Refs.
Rat bone marrow	N/A	200μg	Rat	Intravenous	The day following SCI	Exosome	Suppress the activation of microglia and A1 astrocytes, decrease the levels of TNF-a, IL-1b and IL-6	Promote functional recovery	[194]
Rat bone marrow	N/A	40μg	Rat	Intravenous	30 minutes after SCI	Exosome	Reduce the proportion of A1 astrocytes and the levels of TNF-α, IL-1α and IL-1β	Promote functional recovery	[161]

Abbreviations: EVs, extracellular vehicles; N-NVs, normal MSC-derived nanovesicles; NT-3, neurotrophin-3; IGF-1, insulin-like growth factor 1; Mrc1, recombinant mannose receptor C type 1; Nfe2L2, recombinant nuclear factor erythroid 2 like protein 2; MDA, malondialdehyde; N/A, not applicable.

are needed to monitor the tumorigenic risk of engrafted gene-modified MSCs. Despite these promising avenues of research, further work is needed to improve our knowledge of molecular mechanisms and optimal transplantable conditions. Once these issues are addressed, MSCs are likely to be administered in clinical practice to relieve SCI patient suffering and enhance their quality of life.

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Disclosure

The authors declare that they have no competing interests.

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