

# Mesenchymal Stem Cell Transplantation: Neuroprotection and Nerve Regeneration After Spinal Cord Injury

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**Abstract:** Spinal Cord Injury (SCI), with its morbidity characteristics of high disability rate and high mortality rate, is a disease that is highly destructive to both the physiology and psychology of the patient, and for which there is still a lack of effective treatment. Following spinal cord injury, a cascade of secondary injury reactions known as ischemia, peripheral inflammatory cell infiltration, oxidative stress, etc. create a microenvironment that is unfavorable to neural recovery and ultimately results in apoptosis and necrosis of neurons and glial cells. Mesenchymal stem cell (MSC) transplantation has emerged as a more promising therapeutic options in recent years. MSC can promote spinal cord injury repair through a variety of mechanisms, including immunomodulation, neuroprotection, and nerve regeneration, giving patients with spinal cord injury hope. In this paper, it is discussed the neuroprotection and nerve regeneration components of MSCs' therapeutic method for treating spinal cord injuries.

**Keywords:** spinal cord injury, mesenchymal stem cell, neuroinflammation, neuroprotection, nerve regeneration

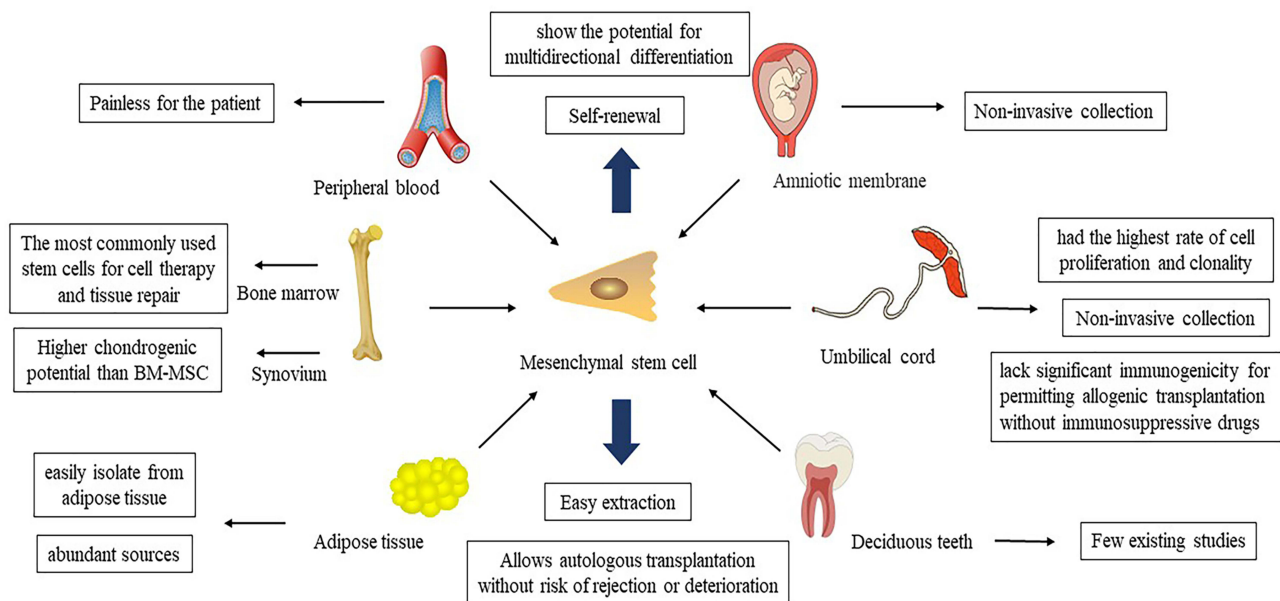
## Introduction

Spinal cord injury (SCI) is a devastating neurological disease, which can lead to temporary or permanent impairment of motor, sensory, and autonomic nerve functions. It is estimated that the global prevalence of SCI has been increasing over the past 30 years, with 236 to 1298 patients per million people in different countries,<sup>1,2</sup> and each SCI patient suffers from both physical and psychological torment and also faces difficulties such as lack of financial resources and broken social relationships.<sup>3</sup> The pathogenesis of SCI can be divided into two stages, the first stage of injury is primary injury (such as from a fall or a traffic accident), and secondary injury ensues as a complex series of abnormal molecular signaling, inflammatory cell infiltration, inflammatory factor release, oxidative stress, vascular changes, and secondary cellular dysfunction hierarchical association reaction, which ultimately leads to apoptotic necrosis of neurons and glial cells, forming a microenvironment unfavorable to nerve regeneration and injury recovery microenvironment, aggravating the injury,<sup>4</sup> and when the injury enters the chronic phase of secondary damage, the already formed glial scar blocks nerve regeneration.<sup>5,6</sup> Patients with SCI experience sensory loss and functional defects below the injured spinal cord level as a result of primary injury and subsequent injury, which influence how severe the condition is.<sup>1,7</sup> No treatment has been able to properly treat SCI and improve the prognosis of SCI patients as of yet. Methylprednisolone decreases oxidative stress and inhibits lipid peroxidation in addition to treat post-SCI neuroinflammation effectively.<sup>8,9</sup> However, using methylprednisolone can lead to serious side effects as sepsis, pneumonia, wound infection, and gastrointestinal bleeding<sup>10</sup>. The glycolipid molecule gangliosides, which are found in neuronal membranes, are used as a neuroprotective agent in the treatment of SCI has several effects, including the prevention of apoptosis and anti-excitotoxic activity. However, studies have shown that after six months of ganglioside treatment, there is no difference in neurological recovery.<sup>6,11</sup> Mesenchymal stem cell (MSC) transplantation, is a novel therapy full of optimism and

potential development, has evolved precisely because the currently available medicines to suppress neuroinflammation and neuroprotective drugs do not achieve the optimal standard of treatment for SCI.

Mesenchymal stem cells (MSCs) are pluripotent stem cells that can be derived from a variety of tissues, including bone marrow, adipose, human umbilical cord blood, and others.<sup>12,13</sup> MSCs have the capacity for multidirectional differentiation and self-renewal, and they can differentiate into end-stage cells such as lipogenic cells, chondrogenic cells, and neuronal cells *in vitro* when subjected to various stimulating factors and induction media.<sup>14–16</sup> These qualities have caused MSCs to gradually gain attention in the fields of medicine and tissue engineering in recent decades, and numerous experiments have now demonstrated that MSCs are a very promising research area and have extensive research significance for the regeneration of various tissues and cells, such as bone, skin, and nerves.<sup>7,17,18</sup> The emergence and growth of MSCs have greatly aided the search for novel treatments for several disorders. MSC transplantation is a frequent first step in the investigation of disease therapeutic techniques that function through direct physical contact between cells, paracrine secretion, transfer of mitochondria, transfer of RNA, and other molecules, among other mechanisms.<sup>19,20</sup> Through these modes of action, MSCs can decrease inflammatory responses, alter immune cell activity, reduce tissue damage and induce regeneration.<sup>21,22</sup>

Numerous studies have demonstrated the capacity for MSCs from various sources (bone marrow, fat, umbilical cord blood, dental pulp, etc.) to treat SCI, which is consistent with a similar mechanism<sup>17</sup> (Figure 1). Different tissue-derived MSCs have varying capacities for differentiation and proliferation.<sup>17,23</sup> Under typical differentiation settings, bone marrow mesenchymal stem cells have good osteogenic and chondrogenic properties, while synovial-derived cells have a higher capacity for chondrogenesis than BM- MSCs.<sup>24</sup> MSCs from synovial and adipose tissue had greater adipogenic potential than MSCs from bone marrow.<sup>24,25</sup> Comparison of the proliferative potential of bone marrow, adipose, and umbilical cord-derived MSCs revealed that umbilical cord blood mesenchymal stem cells were found to have the highest cell proliferation rate and clonogenicity.<sup>26</sup> Different types of MSCs secrete various bioactive substances. For illustration, umbilical cord mesenchymal stem cells (UC-MSCs) secrete more neurotrophic substances (bFGF, NGF, NT3, NT4, and GDNF), whereas bone marrow mesenchymal stem cells (BM-MSCs) and adipose-derived mesenchymal stem cells (Ad-MSCs) secrete more pro-angiogenic substances.<sup>27</sup> Inhibiting the inflammatory response at the injury site, reducing the formation of peripheral glial scar to slow the process of spinal cord injury, enhancing neuroprotection and promoting axon regeneration, and finally reducing neuralgia and promoting functional recovery in patients with SCI are all important functions of various bioactive factors.<sup>28</sup> Many MSCs transplant clinical trials are already in the first stages (Phase I/II), and their feasibility and safety have already been tentatively



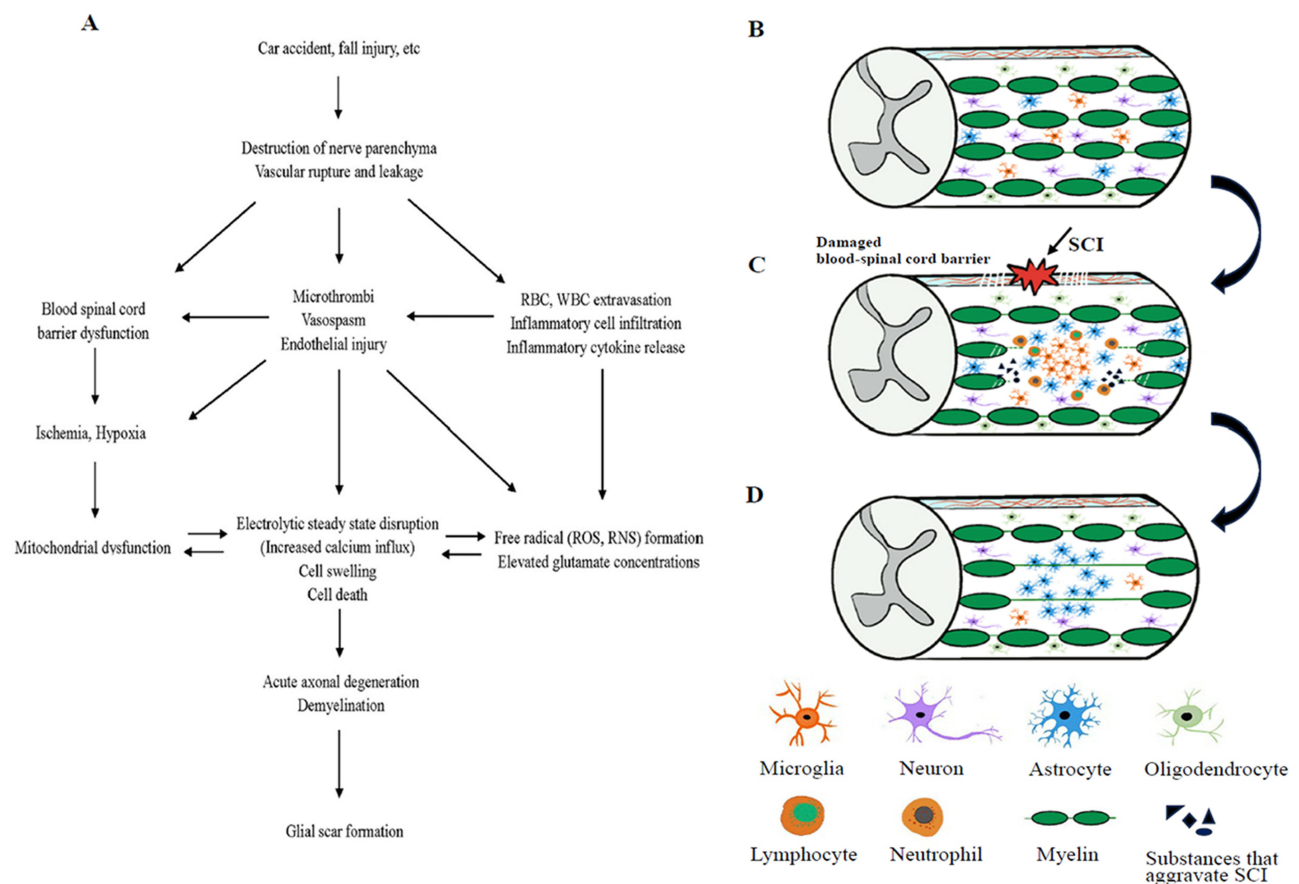
**Figure 1** Mesenchymal stem cells of various origins: Peripheral blood, Bone marrow, Adipose tissue, Amniotic membrane, Umbilical cord, Deciduous teeth, et al. Mesenchymal stem cells are capable of self-renewal and multidirectional differentiation, and different sources of MSCs have some different advantages.

established.<sup>29,30</sup> We will discuss the therapeutic mechanism of MSCs on SCI, concentrating on the role of neuroprotection and nerve regeneration in the mechanism of mesenchymal stem cell transplantation, in order to better understand the therapeutic effect of MSCs on spinal cord injury and simplify follow-up research.

## Pathophysiology of Spinal Cord Injury

The first stage of spinal cord injury (SCI) is the primary injury event, also described as primary injury, which is an injury to the spinal cord from physical forces such as compression, shear, laceration, acute stretch/distraction, and large area impact.<sup>11,27,31</sup> The blood vessels at the wounded site are ruptured and leak during this phase, which also results in damage to the nerve parenchyma and glial structure.<sup>32,33</sup> The secondary injury is the second stage of spinal cord injury (SCI), which is brought on by the primary injury event to start a secondary response that lasts almost the entire duration of SCI. The secondary injury event also causes the spinal cord injury area to grow through a series of complex and related cascades, aggravating SCI<sup>34,35</sup> (Figure 2).

According to the unique characteristics of the various damage periods, the secondary injury occurrences have been divided into three categories: acute, subacute, and chronic.<sup>31,32</sup> After an injury, the acute phase lasts for 48 hours and is characterized by symptoms such as vascular dysfunction, free radical generation, increased calcium inward flow, inflammation, excitotoxicity, and edema.<sup>36</sup> The course of spinal cord injury enters a subacute phase (2–14 days) if the acute phase is not interrupted, which is marked by axonal demyelination, Wallerian degeneration, axonal remodeling, and other symptoms.<sup>32,36,37</sup> It subsequently reaches a chronic phase that persists for the rest of the individual's lifetime, with the chronic phase featuring cystic cavity formation, axonal blight, gliosis, and scar formation after extracellular matrix deposition.<sup>27,38</sup>



**Figure 2** (A) Pathogenesis of spinal cord injury. (B) Normal spinal cord tissue. (C) When a spinal cord injury occurs, the nerve parenchyma and glial structures are damaged, neutrophils, macrophages/microglia, lymphocytes, etc. infiltrate the injured area, and the concentration of compounds that aggravate spinal cord injury (inflammatory cytokines, reactive oxygen species, tissue-degrading enzymes, etc.) rises. (D) Formation of glial Scar.

With ongoing apoptosis or necrosis of neurons and glial cells throughout the response, the many molecular reactions in the secondary injury event are interrelated and interact with one another, all aggravating spinal cord injury to differing degrees.<sup>36,39</sup> Reduced blood flow and extravasation of erythrocytes and leukocytes follow spinal cord injury due to variable degrees of structural malfunction of the blood arteries in the affected area.<sup>32</sup> The extravasation of blood leads to a sustained increase in pressure at the damaged site, combined with the infiltration of peripheral inflammatory cells such as neutrophils, bone marrow-derived macrophages, and lymphocytes into the damaged tissue, the release of inflammatory cytokines (interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-1 $\alpha$  (IL-1 $\alpha$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6)), and vasospasm, micro-thrombosis, persistent bleeding, and other conditions, and eventually blood flow supply is interrupted, damaged tissues become ischemic and hypoxic, and the blood-spinal cord barrier becomes dysfunctional.<sup>36,40,41</sup> In conclusion, the loss of vascular function and structure restricts anticipated restoration techniques and prevents endogenous tissue repair after spinal cord injury.<sup>41,42</sup>

Neuroinflammation contributes significantly to secondary injury, and following SCI, processes associated with inflammation are activated.<sup>43,44</sup> The primary effector cells of the inflammatory response following SCI are activated microglia and recruited macrophages, which can cause neurons and glial cells at the injured region to undergo apoptosis or necrosis.<sup>45</sup> Infiltrating the damaged site sequentially, neutrophils (peaking 1 day after injury), macrophages/microglia (peaking 7 days after injury), and lymphocytes (peaking 9 days after injury) secrete various inflammatory mediators and aid in clearing up cellular debris.<sup>46,47</sup> Tissue levels of inflammatory cytokines peak 6 to 12 hours after injury.<sup>31,48</sup> The subsequently released tissue degradation enzymes, proteases, reactive oxygen species (ROS), and apoptosis-inducing chemicals create a neurotoxic milieu that extends the injury to neighboring healthy tissue and speeds up neuronal and neuronal cell death or necrosis.<sup>49,50</sup> Both positive and negative effects can be attributed to inflammation that develops at the site of the injury. While infiltrating inflammatory cells and releasing inflammatory factors aid in patient repair in the early stages of SCI, their protracted presence worsens neurotoxicity and exacerbates neurological dysfunction.<sup>51</sup>

After blood-spinal cord barrier dysfunction, cell membrane permeability increases, and combined with endothelial injury and inflammatory factors, the ion concentration inside and outside the neuronal and glial cell membranes become imbalanced, with increased extracellular potassium (K<sup>+</sup>) concentrations and increased intracellular sodium (Na<sup>+</sup>) and calcium (Ca<sup>2+</sup>) concentrations, leading to cytotoxic, ionic, and vasogenic edema and persistent edema will eventually lead to massive cellular necrosis.<sup>32,52,53</sup> As a result of the rapid rise in intracellular calcium ion concentration, mitochondria malfunction, and slowed oxidative phosphorylation in an effort to buffer the excess calcium ions.<sup>54,55</sup> Mitochondria are an integral part of the energy metabolism of nerve cells, and their mitochondrial dysfunction has resulted in a lack of energy on which nerve cells depend and an increase in the number of nerve cell deaths.<sup>56</sup> A considerable amount of evidence proves that oxygen radicals are important mediators of secondary damage events in SCI and are involved in oxidative stress to neural tissue, mainly in the form of lipid peroxidation.<sup>54,57</sup> Most of the oxidative stress in damaged neuronal cells initially start with the production of peroxynitrite (PN, an oxidant) in the mitochondria, which produces “oxidative damage” to cellular lipids and proteins, mainly in the form of oxidative attack on polyunsaturated fatty acids of the cell membrane.<sup>58,59</sup> The disruption of mitochondrial respiratory function occurs before, or at least simultaneously with, the production of free radicals in mitochondria, and existing studies have found that mitochondrial dysfunction leads to the emergence of PN, and the rest of the undamaged mitochondria exposed to PN also experience respiratory dysfunction after oxidative stress, with the two interacting to exacerbate neuronal impairment.<sup>60–62</sup> Caused by several factors like physical shock, cell necrosis or apoptosis, and lipid peroxidation, which continually creates cytotoxicity and disrupts cellular ion homeostasis, glutamate, an excitatory neurotransmitter, increases in concentration during SCI.<sup>32,53</sup>

The occurrence of the aforementioned chain of events results in immediate axonal degeneration, oligodendrocyte apoptosis, and persistent apoptosis or necrosis of neurons and glial cells at the site of injury. The stability of axonal function is impacted by the apoptosis of oligodendrocytes, the myelin-forming cells that encourage myelin proliferation and myelin synthesis.<sup>63–65</sup> It also slows down information transmission along the axon and results in axonal demyelination. When secondary injury reaches the chronic stage, astrocytes proceed to proliferate and hypertrophy, migrate along the edges of the severely damaged tissue sites, and secrete a great number of growth inhibitory chondroitin sulfate proteoglycans (CSPGs) to deposit in the microenvironment, eventually forming the central role of the glial scar around the injury’s center. At the same time, fibroblasts also infiltrate the area surrounding the lesion, replacing the extracellular matrix with fibrous connective tissue,

and creating the final chronic stage scar.<sup>31,66–68</sup> The body's natural process of glial scar formation, which initiates and initiates healing after SCI, but some researchers believe it to be one of the barriers to neuronal axon regeneration in the CNS (central nervous system).<sup>69–71</sup> Lesions grow and create cysts as the spinal cord injury progresses, leaving behind microcystic cavities from lingering necrotic or apoptotic cells that eventually form spinal cord cavities, inflicting permanent harm.<sup>31,71</sup>

## MSCs Transplantation

Cell therapy has become a cutting-edge therapeutic approach for spinal cord injuries, and several early clinical trials have shown that cell transplantation is typically possible. However, its effectiveness and long-term safety has not yet been established.<sup>72–74</sup> Among the numerous alternative cells, stem cells have attracted attention because of their capacity for self-renewal and multidirectional differentiation, followed by the selection of different stem cells, mesenchymal stem cells (MSCs) are distinguished by easy isolation, easy preservation, rapid proliferation, low immunogenicity, not involving ethical issues.<sup>27,75</sup> Currently, local injection, intravenous injection, and intrathecal injection are the three most used methods for directly injecting MSCs to treat spinal cord injury.<sup>76–78</sup> While intrathecal and intravenous injections are less invasive but require a large amounts of cells, and the proportion of mesenchymal stem cells reaching the injury site is low.<sup>76,77</sup> local injections can directly transplant a sufficient amount of stem cells to the site of spinal cord injury,<sup>78</sup> However, they may further damage the spinal cord and increase the risk of wound infection.<sup>78</sup> The “homing” capacity of MSCs has garnered interest in experimental experiments using intrathecal and intravenous injections.<sup>79,80</sup> The migration of bone marrow MSCs to the site of injury is regulated by both chemical factors (cytokines, growth factors, etc.) and mechanical factors (mechanical strain, shear stress, etc.).<sup>81–86</sup> Vascular endothelial growth factor-A (VEGF-A) has been shown to stimulate platelet-derived growth factor receptors (PDGFRs) and thereby regulate the migration of human BM-MSCs.<sup>87</sup> Growth factors (PDGF or IGF-1) released at the level of injury attract MSCs to homing, and an increase in inflammatory factors or chemokines at the site of injury also promotes this cellular behavior.<sup>27,88,89</sup> Although local injections can result in spinal cord re-injury, intravenous and intrathecal injections can prevent this. However, cellular localization failure for MSCs moving through “homing” is a possibility. This might have anything to do with the injection time, dose, etc. Further research is required to determine the precise “homing” mechanism and the relationships between the variables.

Cell survival after MSC transplantation influences to some extent the functional improvement after SCI, and in fact, in the damaged spinal cord, the poor microenvironment leads to a low survival rate of transplanted cells.<sup>90,91</sup> Studies are now concentrating not only on direct transplantation of MSCs but also on pretreatment, co-transplantation, and transplantation after genetic modification. This is done to improve the post-transplantation microenvironment and cell survival as well as to enhance the repairing effect of MSC transplantation after spinal cord injury.<sup>92</sup> The secretion and impact of some bioactive substances can be enhanced by MSC transplantation after gene alteration. Glial-derived neurotrophic factor can be expressed more effectively thanks to the microRNA-383 gene, and altering microRNA-383 and its related genes can enhance MSCs' ability to treat spinal cord injuries.<sup>91,93</sup> A medication, biological scaffold, or other cells can be co-transplanted with MSCs to enhance the microenvironment and have a synergistic effect to promote functional recovery.<sup>90,92,94</sup> Pretreating the injury before transplanting MSCs is another option. While the biological scaffold can offer neurotrophic factors, protective growth factors, etc. to promote MSCs to their benefit, the medicine of choice frequently has its own antioxidant, anti-inflammatory, and neurotrophic actions.<sup>94,95</sup> The active ingredient in plumbagin, plumbagin, has been shown in pharmacological studies to have antimicrobial, anti-inflammatory, and anti-cancer effects. Treatment with plumbagin combined with mesenchymal stem cells can significantly improve the recovery of motor function in SCI rats by undoing the inhibition of Nrf2, p-Akt, and p-ERK and the promotion of p-p38 MAPK to exert anti-inflammatory and antioxidant effects.<sup>96</sup> The survival rate of stem cells was increased when they were injected into SCI mice in the form of chitosan (CS) hydrogels loaded with MSCs. As a result, they were able to release a large number of growth factors and anti-inflammatory cytokines to support neural tissue repair and significantly lessen the glial scar, which encouraged axonal growth and nerve regeneration.<sup>97,98</sup> In addition, biological scaffolds are also able to improve difficulties in colonization due to excessive cell spreading after direct transplantation, and collagen scaffolds prepared from fresh bovine tendon membranes have appropriate porosity and nanoscale linear fibers with good adhesion to MSCs, and data suggest that combined appeal scaffolds for rat bone marrow-derived MSC transplantation can not only inhibit chronic scar formation and provide linear neural regeneration priming, but also facilitate the



polarization of macrophages to M2 type for better anti-inflammatory effects.<sup>99</sup> Therefore, the MSC transplantation modality may be an essential research direction for the treatment of spinal cord injury.

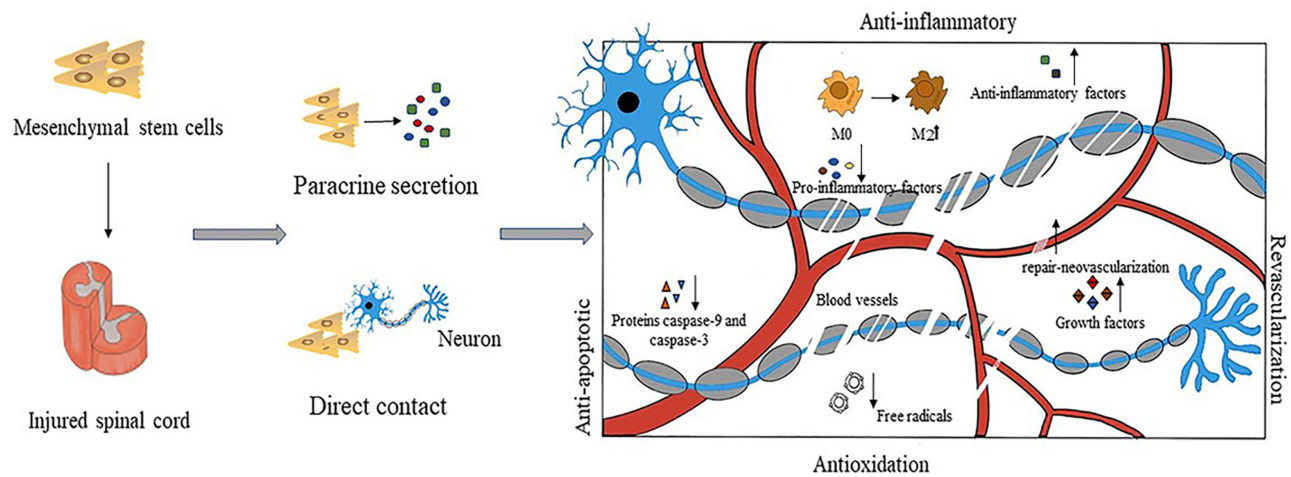
Paracrine secretion and directed differentiation are the two crucial functions of MSCs in repairing injured tissue, however in models of spinal cord injury, paracrine secretion is more likely to occur than directed differentiation.<sup>28,100</sup> Numerous bioactive substances, including as the neurotrophic compounds GDNF and NGF as well as the anti-inflammatory cytokines TNF- $\beta$ 1 and IL-13, are secreted by MSCs.<sup>101–103</sup> MSCs have differentiation potential and can be stimulated to differentiate into neuron-cells in vitro.<sup>103,104</sup> To replace dead cells and restore the integrity of neuronal conduction pathways, researchers have tried to develop MSCs into neuronal cells and glial cells following transplantation into the spinal cord lesion site. However, recent research indicates that there is still a lack of proof for distinction.<sup>105</sup>

Existing research suggests that transplanted MSCs may primarily exert neuroprotective and neuro-regenerative effects through cell-cell interactions and paracrine effects, supporting morphological and functional recovery following spinal cord injury.<sup>106,107</sup> Animals treated with MSCs after transplantation improved motor and sensory capabilities and encouraged the restoration of hind limb function in SCI mice or SCI rats, according to research on animal models of spinal cord injury.<sup>108–110</sup> Clinical trials using MSCs for spinal cord injury has also been conducted recently, and despite their limited frequency, they have so far produced encouraging outcomes. Some SCI patients demonstrated improvement in neurological function when adipose-derived MSCs were extracted from patients' adipose tissue for intrathecal delivery via lumbar puncture.<sup>111</sup> The available data have demonstrated to researchers that MSC transplantation is effective in the treatment of spinal cord injury, even after clinical trial's challenges with a small number of SCI patients who experienced adverse effects (headache, urinary tract infection, nausea and vomiting), as well as a small and heterogeneous number of patients.<sup>112,113</sup>

## MSCs in the Treatment of SCI: Neuroprotection

Neuroprotection is defined as the protection of the structure and function of the injury site and surrounding neurons from further damage by alleviating and attenuating specific events in secondary injury in an attempt to reduce the rate of injury occurrence and mitigate the extent of injury.<sup>11,32</sup> In the acute and subacute phases of spinal cord injury, nerve protection is a crucial treatment goal and the first line of defense that should be put in place as soon as feasible.<sup>42,114</sup> Anti-inflammatory, antioxidant, anti-apoptotic, anti-excitotoxic, and channel blocking can be exploited as breakthrough points for neuroprotection depending on the various events in the secondary cascade response.<sup>115,116</sup> A channel blocker called riluzole will stop excitotoxic cell death by preventing sodium inward flow in injured neurons and restricting presynaptic glutamate release.<sup>31,117</sup> Granulocyte colony-stimulating factor (G-CSF) has been found to increase cell survival and decrease the expression of inflammatory factors (TNF- $\alpha$ , IL-1 $\beta$ ) in the central nervous system.<sup>118</sup> The existing neuroprotective therapies are not limited to this. The therapeutic effects of MSCs on SCI are gaining attention as research advances because they exhibit significant autocrine and paracrine activities, exerting anti-inflammatory and antioxidant effects, preventing neurodegeneration and apoptosis, promoting axonal and myelin regeneration, preventing vascular damage, and enhancing angiogenesis<sup>119–122</sup> (Figure 3).

Anti-inflammatory: Tumor necrosis factor (TNF $\beta$ 1), interleukin (IL-13), IL-18 binding protein, and other substances are secreted by mesenchymal stem cells. MSCs can also control cytokine production in the location of the injury and enhance the inflammatory microenvironment.<sup>122</sup> Mesenchymal stem cells from umbilical cord blood promotes the polarization of M2 macrophages and reduces IL-7 and IFN- $\gamma$ , TNF- $\alpha$ , at the same time, they increased the expression of IL-4 and IL-13.<sup>47,75</sup> Transplantation of murine adipose-derived mesenchymal stem cells inhibit macrophage infiltration and reduce the expression of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6.<sup>22,47</sup> Rat bone marrow mesenchymal stem cells suppress the expression of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ .<sup>21</sup> The research that is currently available indicates that transplanted MSCs can also change the macrophage phenotype from M1 to M2. Microglia and macrophage phenotypes are classified as M1 type (neurotoxic and pro-inflammatory) and M2 type (immune regulation). The bioactive substances released by the latter encourage myelin sheath development and axon growth.<sup>123,124</sup> Reduce the number of M1 macrophages to reduce the production of the inflammatory response, which has a beneficial effect on neuroprotection.<sup>125,126</sup> BM-MSCs can activate M2 macrophages, suppress M1 macrophages, elevate IL-4, and IL-13 levels, and decrease TNF- $\alpha$ , IL-6, and IL-1 $\beta$  levels for immune modulation.<sup>127,128</sup>



**Figure 3** MSCs exhibit anti-inflammatory (promoting the polarization of M2 macrophages, decreasing the expression of pro-inflammatory factors such as IL-7, IFN-, and TNF-, and increasing the expression of anti-inflammatory factors such as IL-4 and IL-13); antioxidant (scavenging free radicals, enhancing host antioxidant defense, and altering cellular bioenergetics); anti-apoptosis (secretion of various protective factors, reduction of caspase-9 and caspase-3 protein levels, etc.); promotion of revascularization (secretion of various growth factors, increase in the density of repair-neovascularization).

**Antioxidation:** One of the efficient damage processes engaged in secondary damage events is lipid peroxidation brought on by oxygen radicals.<sup>54</sup> The constitutive production of the antioxidant enzymes SOD1, SOD2, catalase (CAT), and glutathione peroxidase (GPX), as well as high levels of the antioxidant glutathione, have been linked to MSCs' resistance to oxidative and nitrous stimulation in vitro (GSH). In the animal model of spinal cord injury, MSCs have also been shown to perform an antioxidant role by a wealth of evidence.<sup>129,130</sup> By scavenging free radicals, boosting host antioxidant defenses, and changing cellular bioenergetics, MSCs are currently assumed to lessen oxidative damage.<sup>129,131,132</sup> After adipose MSCs were transplanted, 3-NT, a PN marker, and PC, a protein oxidative stress-related product, significantly decreased at the spinal cord lesion site, trying to show that lipid peroxidation and protein oxidation were reduced after cell transplantation and that MSCs can reduce oxidative stress after injury.<sup>133</sup> The modification of the redox environment and oxidative stress by MSCs, which together promote cytoprotection, also has an anti-inflammatory effect.<sup>134</sup>

**Anti-apoptotic:** After SCI, neuronal and glial cells die as a result of both primary and secondary injury, and the activation of apoptotic pathways also plays a role in cell death.<sup>135</sup> Both the receptor-dependent extrinsic pathway and the intrinsic system, which is influenced by cell-intrinsic events such as DNA damage, hypoxia, and oxidative stress, are involved in apoptosis.<sup>136</sup> In addition to the anti-apoptotic genes, Bcl-2 and the apoptosis-inducing gene Bax are also involved in the regulation of apoptosis after SCI. Caspase-3 and Caspase-8 activation and apoptosis are temporally similar, and Caspase-8 activation is an important step in initiating exogenous pathways after SCI.<sup>137</sup> By lowering apoptosis, mesenchymal stem cell implantation can aid neurological rehabilitation. On days 14 and 28 following the transplantation of olfactory sheath cells combined with bone marrow Mesenchymal stem cells (BM-MSCs), it was discovered that the levels of the proteins caspase-9 and caspase-3 were significantly decreased and the levels of the protein Bcl-2 were significantly increased in the spinal cord of SCI rats.<sup>137</sup> Bone marrow MSCs can also mediate protection against apoptotic injury by secreting protective factors that stimulate neuronal endogenous survival signaling pathways, namely PI3K/Akt and MAPK/ERK1/2 cascade responses.<sup>138</sup> Additionally, the interaction between stressed neurons and BM-MSCs improved neuroprotection even more.<sup>139</sup>

**Revascularization:** Leaky or nonexistent blood vessels cause ischemia, which prevents endogenous regeneration of damaged tissue. Blood vessels play a critical role in spinal cord injury. The ischemia cascade that results from the vascular injury ultimately speeds up cell death and tissue damage by increasing cytotoxic proteolytic enzymes and reactive oxygen species.<sup>40</sup> Whereas endogenous vascular regeneration occurs in the organism during the early stages of spinal cord injury, it is still challenging to re-establish functioning blood vessels at the site of injury.<sup>41,42</sup> When it comes to neuroprotection and nerve regeneration, blood flow reconstruction is essential. Additionally, a healthy blood supply creates a microenvironment that is conducive to the survival of residual tissue and nerve regeneration, which supports functional recovery after spinal cord injury.<sup>41,140,141</sup> MSCs induce angiogenesis by paracrine secretion of vascular endothelial growth factor (VEGF), hepatocyte

growth factor (HGF), platelet-derived growth factor (PDGF), and others.<sup>27</sup> The blood spinal cord barrier (BSCB) leakage was reduced, the density of microvasculature/repair-neovascularization at the injury site was increased, there was extensive remyelination around the injury epicenter, and finally improved functional recovery in SCI rats treated with adult bone marrow-derived mesenchymal stem cells.<sup>142</sup>

## MSCs in the Treatment of SCI: Nerve Regeneration

In the acute and subacute phases of spinal cord injury, prompt neuroprotection can be very beneficial; however, for patients in the chronic phase, nerve regeneration is now more important than neuroprotection.<sup>31</sup> Promoting axonal regeneration after damage is a crucial goal in the treatment of the chronic phase of spinal cord injury since the disruption of central nerve linkages is one of the causes for ongoing dysfunction after SCI.<sup>67,143</sup> The functional recovery of patients with spinal cord injuries may significantly improve with even a little amount of axonal regrowth.<sup>144</sup>

Axon lengthening, axonal sprouting and growth of new axons, the remyelination of nerve cells, and other processes that entail the regeneration and repair of damaged neural tissue (neurons, axons, synapses, and glial cells) after injury are all examples of nerve regeneration.<sup>32,145</sup> Mammalian CNS regeneration is challenging, cannot upregulate the genetic program required for axonal growth as in the regeneration of neurons within the peripheral nervous system, and the capacity for regeneration declines with age due to limited plasticity.<sup>31,144,146</sup> After spinal cord injury, ischemia and hypoxia increase the amount of oxygen free radicals present at the site of injury and lead to the formation of myelin fragments,<sup>40</sup> where it contains inhibitory molecules like Nogo-A protein or myelin-associated glycoprotein (MAG) that stops axon growth in animal models.<sup>27,147</sup>

Collectively, these factors build a microenvironment that is not conducive to axonal regeneration, also referred to as a non-permissive environment. The glial scar, of which astrocytes are the main component, forms a physical barrier that isolates damaged tissue from healthy tissue, leading to impaired axonal regeneration.<sup>31</sup> Although glial scarring has long been considered detrimental to the repair of the injured spinal cord, recent studies have also shown that glial scarring can be protective of the damaged spinal cord,<sup>98,148</sup> and that this discrepancy may be because glial scarring isolates healthy tissue from further damage by inflammatory cells and various toxic molecules in the early stages of injury, but hinders endogenous or treatment-induced axonal regeneration.<sup>98,149</sup> Related investigations have shown how functional recovery in animals with spinal cord injuries are facilitated by enhanced glial scar permeability.<sup>148</sup> By secreting numerous growth-inhibiting chondroitin sulfate proteoglycans (CSPGs), such as Neurocan, Versican, Brevican, PhosphaCan, and NG2, which create a chemical barrier, astrocytes also prevent post-injury repair or regeneration.<sup>31</sup> Therefore, therapies to encourage axonal regeneration within the CNS have concentrated on increasing the intrinsic ability of neurons to renew, improving the environment that is non-permissive for their regeneration, or minimizing the impacts of the double barrier created by astrocytes.<sup>67,144</sup>

Early research into MSC-based regenerative therapies concentrated on their ability to differentiate into neurons or glial cells after transplantation. However, there is currently a lack of conclusive experimental evidence for MSC differentiation *in vivo*.<sup>10,105,150</sup> Nevertheless, transplanted MSCs are still capable of performing a variety of tasks, such as supplying nutritional support, regulating the inflammatory response in the acute phase, and lowering scar tissue inhibition in the subacute and chronic phases to create an environment that is favorable for axonal regeneration.<sup>31,139</sup> Neurotrophic factors have been proven to enhance the growth potential of CNS neurons after injury, and the enhanced ability of neurons exposed to neurotrophic factor (BDNF) or glial-derived neurotrophic factor (GDNF) to overcome the non-permissive environment is mediated by elevated intracellular cAMP levels.<sup>144,151</sup> MSCs are capable of secreting brain-derived growth factor (BDNF), glial cell-derived growth factor (GDNF), nerve growth factor (NGF), NT-1, NT-3, CNTF, and basic fibroblast growth factor (bFGF), leading to the speculation that transplanted MSCs may enhance the intrinsic growth propensity of damaged neurons by secreting neurotrophic factors.<sup>27</sup> In addition to improving intrinsic growth propensity, neurotrophic substances help ameliorate the existing nonpermissive environment by acting as antioxidants, anti-inflammatory agents, and BDNF can act against oxidative stress to increase neuronal survival.<sup>148,152</sup> The glial scar that astrocytes created after transplanting MSCs might also be modified.<sup>153</sup> According to studies, transplanting MSCs into SCI rats prevents the creation of glial scars and alters the reactive astrocytes' shape, which combined create an ideal microenvironment for axonal regeneration.<sup>153,154</sup>

Furthermore, another experiment using human bone marrow-derived MSCs to treat SCI rats showed that the treatment group had a lower density of GFAP-positive scars than the control group, which formed a loose glial scar.<sup>148</sup> The attractive



effect can be seen in experiments using dogs as a model of SCI, where adipose mesenchymal stem cells and chondroitinase ABC (a bacterial enzyme) work together to degrade CSPGs. The results of this experiment showed a significant reduction in the reactive astrocyte marker GFAP and a reduction in scar formation at the injury site.<sup>155</sup> Researchers were motivated to investigate the causes of these effects after learning that BM-MSCs could improve motor function by reducing the activation of TGF- $\beta$ /Smads signaling in astrocytes. Since TGF- $\beta$  can mediate the formation of glial scars by activating Smads, it is hypothesized that BM-MSCs can prevent scarring after injury by controlling the TGF- $\beta$ /Smads signaling conduction pathway.<sup>153,156,157</sup> Further research is required because the precise and intricate mechanism is still unknown.

## Conclusions

Spinal Cord Injury (SCI) is a serious, prolonged and irreversible injury. As a result, a great deal of academics and professionals in the medical field are eager to discover secure and efficient treatments for spinal cord injuries. Numerous preclinical and clinical studies have demonstrated the effectiveness of Mesenchymal stem cell (MSC) in the treatment of SCI. The effectiveness of MSC for the treatment of SCI has now been established by a large number of preclinical and clinical studies. The anti-inflammatory, anti-oxidant, anti-apoptotic, and increased blood flow that MSC transplantation provides protects the nerves. It also increases intrinsic neuronal growth potential, boosts non-permissive settings, and alters glial scarring to support regeneration. Future studies may need to further investigate more specific therapeutic mechanisms as well as better methods of transplanting MSC (pre-treatment, gene modification and combination therapy, and others) because the therapeutic mechanism of MSC transplantation is not fully understood and because issues like inaccurate cell localization and a low survival rate after direct cell transplantation exist.

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