



Mesenchymal stem cell-based therapy for peripheral nerve injuries: A promise or reality?

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Abstract

Peripheral nerve injuries (PNI) that result in nerve gaps represent a major clinical challenge, frequently leading to long-term disability and a diminished quality of life for affected individuals. Despite advances in surgical techniques, functional recovery remains limited, highlighting the need for innovative therapeutic strategies. Mesenchymal stem cells (MSCs) have emerged as a promising avenue for nerve repair due to their regenerative, immunomodulatory, and neuroprotective properties. Thus, this review explored current approaches utilizing MSCs in the treatment of PNI, emphasizing their potential to enhance nerve regeneration and functional recovery. Furthermore, tissue engineering and transdifferentiation of MSCs into Schwann-like cells offer a versatile strategy to optimize therapeutic effects, paving the way for personalized medicine. Nevertheless, challenges persist regarding the clinical application of MSCs in PNI, including transplant safety, delivery methods, optimal dosing, and ethical considerations. A deeper understanding of the mechanisms underlying MSC action in PNI may contribute to more effective treatment protocols in the management of peripheral nerve defects.

Key Words: Cell-based therapies; Extracellular vesicles; Mesenchymal stem cells; Nerve guidance conduits; Nerve regeneration; Regenerative medicine

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Core Tip: Mesenchymal stem cells (MSCs) offer a promising therapeutic approach for peripheral nerve injuries involving nerve gap by promoting axonal regeneration, modulating inflammation, secreting neurotrophic factors, and exhibiting transdifferentiation capacity. These properties position MSCs as a compelling alternative to conventional treatments. However, challenges still exist for the clinical use of MSCs, requiring further research to fully unlock their therapeutic potential and translate these advancements into effective nerve regeneration strategies.

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INTRODUCTION

Peripheral nerve injuries (PNI) are relatively common and can result in debilitating consequences, including neuropathic pain, motor and sensory dysfunction in affected segments, and a substantial reduction in patients' quality of life[1,2]. PNI can result from various etiologies, including traumatic injuries (*e.g.*, accidents, fractures), iatrogenic causes (*e.g.*, surgical complications), infections, chronic nerve compression, and autoimmune disorders[3,4].

Unlike the central nervous system, the peripheral nervous system (PNS) has the capacity for regeneration after injury, primarily due to the plasticity of Schwann cells (SCs)[5]. These cells proliferate, differentiate into a repair phenotype, and secrete a variety of neurotrophic factors and cytokines, creating a microenvironment conducive to neuroregeneration[6]. However, despite the inherent regenerative capacity of the PNS, spontaneous recovery is often insufficient, particularly in cases of extensive nerve damage or long-gap injuries[7].

The management of long-gap nerve injuries remains challenging, with autograft transplant as the standard approach for addressing PNI[8]. Despite advances in microsurgical techniques, this approach has inherent limitations, such as donor site morbidity and the challenge of achieving full recovery[9,10]. As a result, there is a pressing need for innovative treatments that can enhance nerve regeneration and improve functional outcomes.

In recent years several novel approaches for PNI repair have emerged, demonstrating positive effects in promoting neuroregeneration. However, fully restoring nerve function remains a challenge[11]. In this context cell-based therapies have emerged as a promising alternative, with mesenchymal stem cells (MSCs) garnering significant interest due to their regenerative potential[12]. MSCs possess properties, such as the ability to differentiate into various cell types, secrete trophic factors that promote tissue repair, and modulate the immune response, thereby creating a favorable environment for nerve regeneration[13]. Additionally, MSCs have been combined with tissue engineering techniques, which enhance their therapeutic effects in PNI repair[14]. Given these considerations, this narrative review aimed to comprehensively assess the therapeutic potential of MSCs in PNI regeneration, critically evaluating recent advancements, persisting challenges, and future directions for optimizing MSC-based therapies in nerve repair.

SEARCH STRATEGY

A comprehensive literature search was conducted using the PubMed database to identify relevant studies published up to March 2025. The search strategy incorporated keywords including "mesenchymal stem cells", "peripheral nerve injury", "nerve regeneration", "extracellular vesicles", "Schwann-like cells", "transdifferentiation", "nerve guidance conduits", and "genetic engineering" as well as various combinations of these terms. The initial search was restricted to studies published between 2015 and 2025. To ensure thorough and up-to-date coverage, a subsequent broader search was performed without date limitations. Studies were considered eligible if they investigated the role, underlying mechanisms, or therapeutic potential of MSCs or their derivatives in the context of PNI. Articles that did not focus on MSC-based approaches or were unrelated to peripheral nerve repair were excluded.

PNI

PNI remains a significant cause of disability, as it can lead to the loss of motor and sensory functions, as well as neuropathic pain, compromising the quality of life of patients[15,16]. PNI can have different origins, including trauma,

infections, iatrogenic injuries, tumors, and autoimmune conditions[17,18]. Every year millions of people are affected by PNI[19]. In the United States, approximately 43.8 people per million suffer traumatic nerve injuries annually[20]. A study in the country revealed that more than 2% of patients with limb trauma present with PNI[21]. Additionally, traumatic brachial plexus injuries can result in an indirect cost of over \$1.1 million per patient[22].

CLASSIFICATION OF PNI

The success of PNI regeneration depends on several factors, with the severity of the injury being one of the most determining points. Traditionally, PNI are classified according to Seddon[23] in 1943 and Sunderland[24] in 1951 (Table 1 and Figure 1). Seddon's classification consists of three categories: neuropraxia; axonotmesis; and neurotmesis. Sunderland complements this approach by subdividing the injuries into five grades based on histopathological characteristics ranging from the mildest (grade I) to the most severe (grade V). These grades correspond, respectively, to neuropraxia and neurotmesis in Seddon's classification.

Neuropraxia is characterized by focal demyelination without involvement of the axon or connective structures of the nerve. Grades II, III, and IV represent subdivisions of axonotmesis: In grade II, there is damage to the axon and myelin sheath; in grade III, involvement of the axon, myelin and endoneurium; and in grade IV, damage to the axon, myelin, endoneurium, and perineurium. Neurotmesis (grade V of Sunderland) involves complete nerve transection and loss of nerve continuity.

ENDOGENOUS REGENERATION

After PNI various cellular, molecular, and microstructural events occur to promote axonal regeneration[27] (Figure 2). In the distal segment of the injured axons, Wallerian degeneration begins, a process involving degradation of myelin, axonal degeneration, and proliferation of SCs, creating a microenvironment conducive to neuroregeneration[28]. Following by an influx of extracellular calcium into the axons, which results in the activation of calpain proteases, responsible for the degradation of axonal neurofilaments[11].

SCs transdifferentiate into a repair phenotype, playing a crucial role in regeneration[29,30]. They proliferate, phagocytize axonal and myelin debris, and recruit immune system cells to the injury site[31,32]. Additionally, SCs release cytokines such as interleukin (IL)-1 α , IL-1 β , monocyte chemoattractant protein-1, and tumor necrosis factor α , promoting the recruitment of macrophages that assist in vascularization and degradation of myelin remnants[33].

Parallel to the degeneration process, axonal regeneration begins. SCs secrete several neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), glial cell line-derived neurotrophic factor (GDNF), and nerve growth factor (NGF), which play a crucial role in neuronal regeneration[34]. Furthermore, these cells reorganize within their basal lamina, forming the Büngner bands, which act as guides for axonal growth[35]. Although the PNS has regenerative capacity, mainly due to the plasticity of SCs, regeneration is often unsatisfactory[5,36], requiring interventions to attempt a more effective recovery.

STRATEGIES FOR PERIPHERAL NERVE REGENERATION

Injuries involving nerve defects are challenging and can result in severe functional deficits. Some therapeutic approaches include neurorrhaphy, nerve grafts, and pharmacological and physical therapies[11]. However, motor and sensory recovery is still limited, which drives the search for new therapeutic strategies.

Neurorrhaphy is indicated when the nerve ends can be approximated without tension or scars that would hinder regeneration[37]. However, this technique is limited to small gap defects, as excessive tension compromises axonal regeneration[38]. Autografts are the standard approach for segmental nerve defects greater than 3 cm[11,39]. Despite their effectiveness this technique has drawbacks, such as the need to remove healthy nerve tissue, limited tissue availability, and the risk of scar formation and neuroma development[40]. Allografts can be used as an alternative, employing nerves from donors or cadavers. However, this approach requires systemic immunosuppression to reduce the risk of graft rejection, limiting its clinical application[11,41].

Given the limitations of conventional methods, new strategies are being explored in PNI research, such as the use of nerve guidance conduits (NGCs) to direct axonal regeneration and reduce the need for grafts[42]. Moreover, cell therapies are gaining attention, including the use of SCs due to their essential role in nerve regeneration. Nevertheless, their clinical application still faces challenges, such as the need for a donor nerve for procurement, time required for expansion, potential low survival at the site, and susceptibility to environmental factors[1,43]. In this context MSCs have emerged as a promising alternative, offering advantages such as multipotency, plasticity, and the ability to modulate the regenerative microenvironment.

Table 1 Summary of the Seddon[23] and Sunderland[24] classification of peripheral nerve injury					
Classification					
Seddon	Neuropraxia	Axonotmesis	Axonotmesis	Axonotmesis	Neurotmesis
Sunderland	I	II	III	IV	V
Injury	Focal demyelination	Axon and myelin damage	Axon, myelin and endoneurium damaged	Axon, myelin, endoneurium, and perineurium damaged	Complete nerve transection
Spontaneous recovery	Yes. Hours to a few weeks	Yes. Weeks to months	Not probable	Highly improbable	Spontaneous functional recovery is not possible
Surgical intervention	Normally not	Normally not	May be necessary	Necessary	Necessary

Adapted from Hussain *et al*[25] and Maugeri *et al*[26].

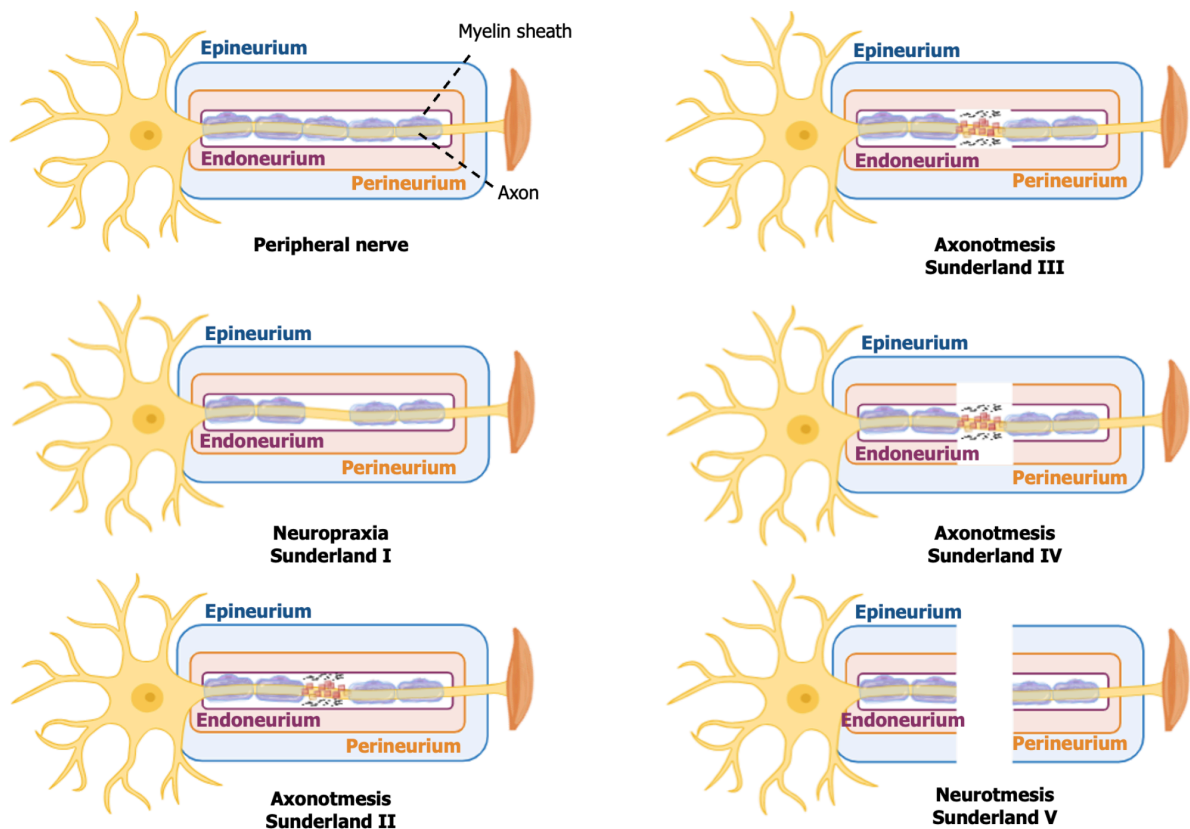


Figure 1 Schematic representation of the grading systems for peripheral nerve injuries. Neuropraxia (Sunderland: Grade I) involves focal demyelination. Axonotmesis is subdivided into grade II (axon and myelin damage), grade III (axon, myelin, and endoneurium damage), and grade IV (axon, myelin, endoneurium, and perineurium damage). Neurotmesis (grade V) is complete nerve transection. Created in BioRender. Amorim, R. (2025) <https://BioRender.com/z6uzrjj>.

MSCS

MSCs are mesodermal-origin multipotent cells that can be isolated from various adult tissues. They have a broad differentiation potential into multiple cell lineages, making them a promising option for therapeutic applications[44]. The MSCs can be obtained from different sources, including adipose tissue, bone marrow, dental pulp, amniotic membrane, umbilical cord, Wharton’s jelly, and skeletal muscles[45]. The International Society for Cellular Therapy established minimum criteria for the characterization of human MSCs, which include plastic adherence, the presence of specific markers (*e.g.*, CD105, CD73, and CD90), the absence of others (*e.g.*, CD34, CD45, CD79 α , and HLA-DR), and the ability to differentiate into chondrogenic, osteogenic, and adipogenic lineages[46]. Some markers, such as CD271, have been adopted following this standardization, and the differentiation capacity into all three germ layers has already been demonstrated[47-49]. However, these criteria have not yet been revised. The main mechanisms of action of MSCs involve cell-cell contact, stimulation of proliferation, and differentiation of different cell types, as well as mitochondrial transfer, release of soluble factors, and extracellular vesicles (EVs)[13,50,51] (Figure 3).

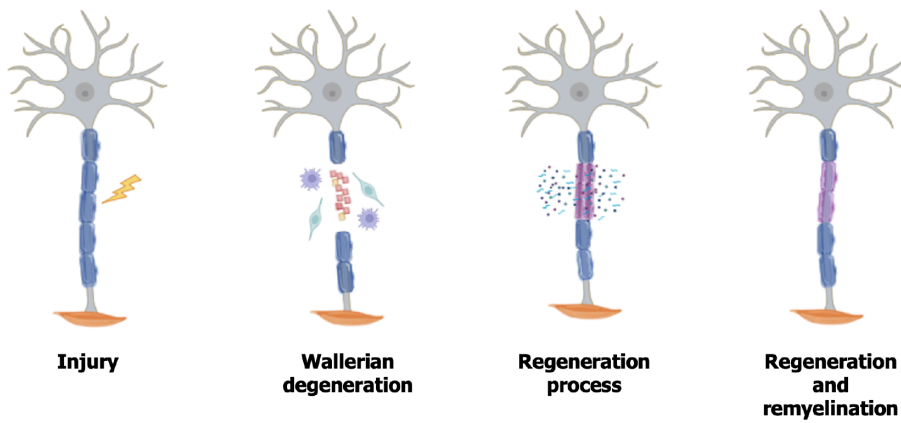


Figure 2 Endogenous regeneration process of the peripheral nervous system. Following injury, Wallerian degeneration occurs, and Schwann cells proliferate and transdifferentiate while acting alongside macrophages to remove cellular and myelin debris. For regeneration Schwann cells form Büngner's bands and secrete neurotrophic factors that support axonal growth. Created in BioRender. Amorim, R. (2025) <https://BioRender.com/z6uzrjj>.

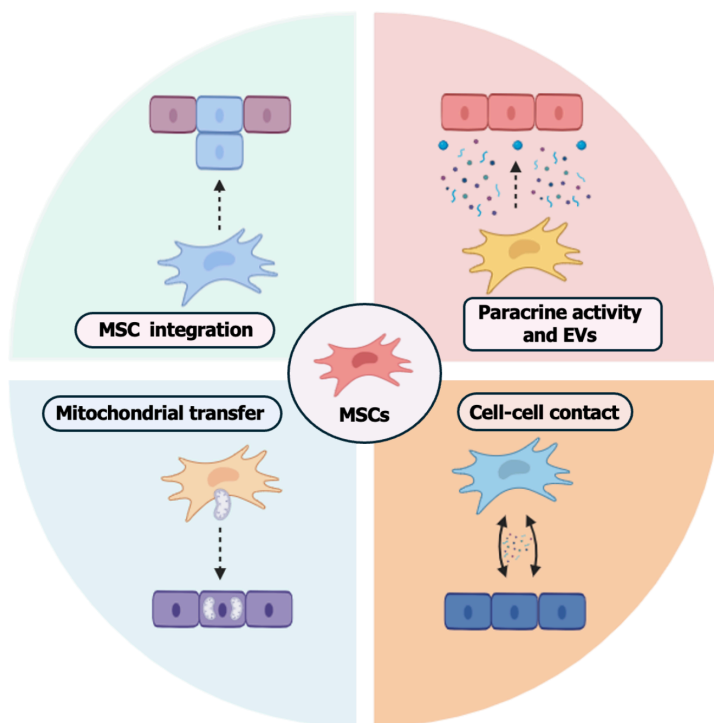


Figure 3 Schematic illustrating of the main mechanisms of mesenchymal stem cell action. Mesenchymal stem cell integration, paracrine activity, release of extracellular vesicles, mitochondrial transfer, and cell-cell contact. Created in BioRender. Amorim, R. (2025) <https://BioRender.com/z6uzrjj>. MSCs: Mesenchymal stem cells; EVs: Extracellular vesicles.

PARACRINE EFFECT

MSCs have immunomodulatory, anti-inflammatory, anti-apoptotic, and neuroprotective features[52], making them a promising approach for peripheral nerve regeneration. Neuroprotection mediated by MSCs is associated with the production of factors, including NGF, BDNF, GDNF, fibroblast growth factor 2 (FGF-2), CNTF, insulin-like growth factor, and hepatocyte growth factor, and neurotrophins that promote neuronal survival and assist in functional recovery after nerve injuries[12,53,54].

In addition, the immunomodulatory effects of MSCs are attributed to the secretion of molecules such as transforming growth factor beta (TGF- β), prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase, nitric oxide, IL-6, and IL-10[55,56]. They also play an angiogenic role through the release of vascular endothelial growth factor (VEGF), inhibitor of metalloproteinase 18, and angiopoietin 1[45]. However, the immunomodulatory potential may vary between species and tissues and be influenced by the presence of inflammatory or anti-inflammatory stimuli[57].

EVS

EVs are classified based on their size and biogenesis[58]. They can be divided based on their dimensions, being categorized as small EVs and large vesicles[59]. MSCs release EVs that play an essential role in intracellular communication and contribute to immunomodulation and neuroprotection[60,61]. Although the exact mechanisms underlying the therapeutic effects of EVs have not yet been fully elucidated, it is known that they act as carriers of mRNA and microRNA (miRNA), influencing cellular processes[62]. A study demonstrated that adipose tissue-MSC-exosomes can stimulate the proliferation of SCs and contain various factors, such as BDNF, GDNF, NGF, insulin-like growth factor 1, and FGF, which support nerve regeneration[63].

The use of EVs derived from MSCs demonstrates efficacy equivalent to that of their parental cells[54,64] and offers advantages over cell therapy, including low immunogenicity, ability to cross the blood-brain barrier[65], and potential to be used as drug delivery systems[66]. Moreover, the use of these EVs has shown promising results in the treatment of PNI in laboratory animal models. Studies have demonstrated that EVs derived from different sources of MSCs, such as bone marrow-derived MSCs[67], adipose tissue-derived MSCs (AT-MSCs)[63,68], umbilical cord-derived MSCs[69,70], and gingival MSCs[71], improved nerve regeneration *in vivo*. However, the clinical application of EVs still faces challenges, such as the lack of standardization in collection and isolation methods, variation in their biological characteristics, and difficulties in large-scale production for therapeutic purposes[72].

OTHER MECHANISMS

MSCs exhibit immunomodulatory effects through direct contact with innate and adaptive immune cells[73]. The proximity of MSCs allows the transfer of molecules such as miRNA, peptides, and mitochondria to the cells[74]. It has been shown that MSCs can modulate the immune response by interacting with proinflammatory macrophages, promoting the conversion of the M1 phenotype to M2 and reducing T cell proliferation[75,76]. Additionally, direct contact with T lymphocytes can induce functional changes in these cells and stimulate the release of TGF- β and PGE2 [76].

Mitochondria are essential for adenosine triphosphate production, regulation of oxidative phosphorylation, and control of cellular apoptosis[77]. An *in vitro* study demonstrated that MSCs can transfer healthy mitochondria to neurons subjected to oxidative injury, promoting increased neuronal survival and improving cellular metabolism[78]. Additionally, it was observed that the administration of mitochondria derived from bone marrow MSCs in mice with sciatic nerve crush injuries promoted axonal regeneration[79].

MSC DELIVERY IN PNI

Different routes

Several MSC delivery strategies have been explored for the treatment of PNI, aiming to maximize their regenerative efficacy (Table 2)[80-85]. Delivery routes include intramuscular and intravenous injections[80]. Intravenous administration allows systemic distribution but is limited by capillary retention in organs such as the lungs, reducing the number of MSCs that reach the injury site[80]. Additionally, intraperitoneal administration has also been investigated as an alternative route in experimental PNI in a rodent model[81]. More targeted approaches, such as epineural[82], perineural [83], and subepineural[84], administrations have been studied for offering a localized delivery, promoting direct contact with the injured nerve tissue. However, there are still controversies regarding whether microinjections may result in ultrastructural trauma and reduced cell viability[86].

Combination of MSCs with NGCs

NGCs have emerged as a promising alternative for the regeneration of PNI, particularly in cases involving large gaps between the injured nerve stumps[87]. These devices provide physical support and create a favorable microenvironment for axonal regeneration, promoting the directed growth of nerve fibers[88]. NGCs can be made from autogenous and allogeneic biological materials, as well as non-biological materials[89]. The materials used can be synthetic, natural, or a combination of both, and their selection is based on properties such as biocompatibility, biodegradability, porosity, mechanical strength, and the ability to promote cellular interaction[90]. Among natural materials collagen, chitosan, fibrin, hyaluronic acid, methacrylated gelatin, and silk stand out[91]. Among synthetic materials poly(lactic acid), polyglycolic acid, poly(lactic-co-glycolic acid), and polycaprolactone show promise[91]. Besides the material selection, NGCs can present different designs, such as porous, grooved, with fiber or hydrogel fillers, hollow/non-porous, and multi-channel, which vary according to the specific needs of each application (Figure 4)[42].

Technological advances have expanded the possibilities for the design and fabrication of NGCs. Techniques such as electrospinning, freeze/dry processing, dip-coating, centrifugal casting, phase separation, and three-dimensional (3D) printing have enabled the creation of customized conduits[92]. 3D printing enables the construction of NGCs with complex architecture and adjustable mechanical properties, creating a more controlled and biomimetic environment for nerve regeneration[93].

The combination of NGCs and MSCs holds significant promise for the treatment of PNI. Research has highlighted encouraging outcomes from this approach, including enhanced axonal regeneration and improved functional recovery (Table 3). Despite the advancements in the use of NGCs and MSCs, this approach has not always been superior to the use

Table 2 Transplantation of mesenchymal stem cells in peripheral nerve injuries

Cell	Delivery	Models	Cell numbers	Outcome	Notes	Ref.
AT-MSCs (canine)	Perineural	Rat sciatic nerve crush	1×10^6	Improved electro-physiological and motor recovery	Assessment performed for 4 weeks	[83]
AT-MSCs (rat)	Intraperitoneal	Rat sciatic nerve transection and suture repair	2×10^6	Improvement in nerve regeneration and functionality	No difference was observed in compound muscle action potential latency between the saline and MSC groups	[81]
BM-MSCs (rat)	IM and IV	Small gap neurorrhaphy (rat sciatic nerve)	1×10^6	Improvements in the sciatic function index, nerve conduction velocity, and myelin sheath thickness	The IM group showed better results compared with the IV group	[80]
BM-MSCs (rat)	IV and epineural	Rat sciatic nerve transection and suture repair	IV: 1×10^6 . Epineural: 5×10^4	Enhancement in the recovery rate of compound muscle action potential amplitudes and axon counts	IV administration showed a more pronounced effect on electromotor recovery, while epineural injection was more effective in increasing fiber counts	[82]
BM-MSCs (rat)	Local injection and IV	Rat sciatic nerve transection/repair and individual nerve transection/repair	5×10^6	Improvements in motor function recovery in both models	The motor function recovery was significantly more pronounced in the individual nerve transection/repair model compared with the sciatic nerve transection/repair model	[85]
BM-MSCs (rat)	Subepineural	Rat sciatic nerve transection and surgical coaptation	5×10^5	Improvements in the sciatic function index	The group treated with MSCs and immunomodulators had better functional recovery than the group treated with MSCs alone. Immunomodulation using LPS and FK506 can improve MSC survival after transplantation	[84]

AT-MSCs: Adipose tissue-derived mesenchymal stem cells; BM-MSCs: Bone marrow-derived mesenchymal stem cells; MSCs: Mesenchymal stem cells; IM: Intramuscular; IV: Intravenous; LPS: Lipopolysaccharide.

of autografts in nerve regeneration, necessitating further research to address existing limitations.

The integration of MSCs with NGCs can be achieved through various methods. One approach involves seeding the cells onto the conduit after fabrication, which offers flexibility but may result in low cell adhesion[107]. Alternatively, MSCs can be encapsulated in hydrogels before being integrated into 3D-printed structures or incorporated through bioprinting, which ensures better cell arrangement and loading efficiency but requires precise optimization of printing parameters[107].

Bio 3D-MSC technology refers to a cutting-edge approach that combines MSCs with 3D bioprinting to create scaffold-free NGCs. This technology enables the fabrication of complex, cell-laden structures, utilizing MSC spheroids as the unique cellular component[94]. It can be tailored to the patient's needs using a controlled system and does not contain foreign materials[108]. Additionally, studies demonstrate that this technology promotes nerve regeneration and may serve as a promising treatment option for PNI[95,96] (Table 3). Challenges remain to be addressed regarding bioprinting. These include accurately replicating the microanatomy of nerve tissue, developing a 3D environment capable of supporting multiple cell types and achieving more precise control over the mechanical and biochemical properties of the conduit[109].

TRANSDIFFERENTIATION INTO SCHWANN-LIKE CELLS

The transdifferentiation of MSCs into Schwann-like cells (SLCs) has been widely studied as an alternative to SC transplantation for the treatment of PNI. Transdifferentiation is commonly induced using chemical and growth factors, including beta-mercaptoethanol, retinoic acid, forskolin, basic FGF, platelet-derived growth factor, and heregulin[110, 111]. Based on this approach, other methodologies have been developed incorporating glial growth factor-2[112], folic acid[113], and dihydrotestosterone[114] into the induction cocktails.

Moreover, there are several protocols in the literature that use neurotrophic factors, co-culture[115], glucocorticoids, insulin, progesterone[116], electrostimulation[117], cell imprinting[118], intermittent induction[119], 3D matrices[120], conditioned medium obtained from peripheral nerve explants[121], and exosomes[122]. The transdifferentiation process is regulated by various mechanisms, including transcription factors and miRNAs[72]. The involvement of miRNA-21-5p in this process has been demonstrated[123], while the overexpression of miRNA-214 in SLCs may enhance their effects on nerve repair[72]. Several markers are used to characterize SLCs after transdifferentiation, as reviewed previously[124]. However, there is still no consensus on which ones should be adopted. Despite the promising therapeutic potential of SLCs derived from different sources of MSCs (Table 4), significant challenges persist. Reaching a consensus on cell characterization, ensuring cell quality and phenotypic stability, and assessing long-term safety are crucial to advancing

Table 3 Combination of mesenchymal stem cells and nerve guidance conduits for the treatment of peripheral nerve injuries

Cell source	Conduits	Models	Cell numbers	Outcome	Notes	Ref.
AT-MSCs (human)	Polycaprolactone	15 mm gap in the rat sciatic nerve	1×10^6	Improvement in axonal growth and expression of factors that aid in reinnervating muscle tissue	Poloxamer hydrogel + AT-MSCs promote more axonal growth than when AT-MSCs were delivered without it	[97]
AT-MSCs (rat)	Fibrin gel	A 20 mm segment of the sciatic nerve was excised in rats and sutured back in the reverse direction	3×10^6	Enhanced remyelination, axonal regeneration, and functional recovery	The use of AT-MSCs resulted in a significant improvement compared with the autologous nerve graft group	[98]
AT-MSCs (rat)	Silicone tube	10 mm gap in the rat sciatic nerve	1×10^6	Improvement in the recovery of walking function	The combination of AT-MSCs with platelet-rich fibrin showed better results than AT-MSCs alone	[99]
AT-MSCs (canine)	Polycaprolactone + heterologous fibrin biopolymer	12 mm gap in the rat sciatic nerve	1×10^6	Improvement in functional motors and electrophysiological recovery	The improvements observed were not significantly different from those obtained with autografts	[100]
AT-MSCs (rat)	Chitosan + acellular nerve	10 mm gap in the rat sciatic nerve	Unknown	Improvement in neurological and motor function and in the quality of the myelin sheath	At 12 weeks there was no significant difference in the degree of recovery compared with the autograft group. The electrophysiological characteristics were also similar to those of the autograft	[101]
BM-MSCs (rat)	Polycaprolactone + fibrin sealant	6-7 mm gap in the rat sciatic nerve	3×10^5	Improvement in the regeneration process, modulation of SCs, and motor functional recovery	There was no significant difference in the total estimated number of regenerated fibers between the groups	[102]
BM-MSCs (rat)	Bio 3D conduits from BM-MSCs	5 mm gap in the rat sciatic nerve	3×10^5	Improvements in nerve regeneration, kinematic analysis, and morphological parameters	No neuroma formation was found 8 weeks after the surgery. The Bio 3D group exhibited a higher abundance of myelinated axons compared with both the silicone NGC group and the silicone NGC with MSCs group	[96]
UC-MSCs (human)	Longitudinally oriented collagen conduit	A 35-mm-long segment of the dog's sciatic nerve was removed	1×10^6	Improvements in axonal regeneration and functional recovery	Nerve regeneration was inferior to the autologous nerve graft group	[103]
UC-MSCs (human)	Bio 3D conduits from UC-MSCs	5 mm gap in the rat sciatic nerve	3×10^5	Improvements in kinematic analysis, as well as in the diameters and number of myelinated axons	The Bio 3D conduit showed better results than the silicone tube and demonstrated nerve regeneration comparable with the autologous group. UC-MSCs in the Bio 3D conduit gradually diminished until week 8	[95]
WJ-MSCs (human)	Acellular nerve	10 mm gap in the rat sciatic nerve	1×10^6	Improvements in myelin and axon regeneration, nerve function, and muscle atrophy reduction	Evaluation at 8 weeks. Increased in both the proportion of myelin in the tissue and myelin thickness, resembling the results seen in the autograft group	[104]
WJ-MSCs (human)	Poly (DL-lactide-e-caprolactone) copolyester	10 mm gap in the rat sciatic nerve	2×10^6	Improvements in nerve regeneration, functional recovery, and increased expression of neurotrophic and angiogenic factors	Evaluation at 12 weeks	[105]
OM-MSCs (rat)	Chitosan	About 10 mm gap in the rat sciatic nerve	1×10^6	Improved in nerve regeneration, motor performance, sciatic indexes, and lower gait dysfunction	The treated groups did not show a significant difference in the stereological results	[106]
GMSCs (human)	Bio 3D conduits from GMSCs	A 5 mm gap in the buccal branch of the rat facial nerve	4×10^4	Improvements in nerve regeneration and functional recovery	Effects comparable to the autograft group	[94]

AT-MSCs: Adipose tissue-derived mesenchymal stem cells; BM-MSCs: Bone marrow-derived mesenchymal stem cells; UC-MSCs: Umbilical cord-derived mesenchymal stem cells; WJ-MSCs: Wharton's jelly-derived mesenchymal stem cells; OM-MSCs: Olfactory mucosa-derived mesenchymal stem cells; GMSCs: Gingiva-derived mesenchymal stem cells; NGC: Nerve guidance conduit; SCs: Schwann cells; 3D: Three-dimensional.

Table 4 Transplantation of Schwann-like cell-derived mesenchymal stem cells in peripheral nerve injuries

Starting cell	Delivery	Models	Method of transdifferentiation	Cell numbers	Effects	Notes	Ref.
AT-MSCs (rat)	Nerve fibrin conduit	10 mm gap in the rat sciatic nerve	Chemical and growth factors	2×10^6	Improvement in axonal regeneration	No undifferentiated MSC transplantation group. Similar outcomes were observed between the SLCs derived from AT-MSCs and BM-MSCs 2 weeks post-transplantation	[125]
AT-MSCs (rat)	Nerve fibrin conduit	10 mm gap in the rat sciatic nerve	Chemical and growth factors	2×10^6	Improvement in axonal and fiber diameters and reduction in muscle atrophy (gastrocnemius)	No undifferentiated MSC transplantation group. SLCs derived from AT-MSCs were more effective than those derived from BM-MSCs after 4 months	[126]
AT-MSCs (rat)	Silicone tube	10 mm gap in the rat sciatic nerve	Chemical and growth factors	1×10^6	Improvement in axonal regeneration, sciatic function index, and myelination	AT-MSCs and SLCs exhibited a similar impact on nerve regeneration 6 months post-transplantation	[127]
AT-MSCs (human)	Local injection	Tibial crush in rats	Chemical and growth factors	1×10^5	Improvement of survival and myelin formation rates	AT-MSCs secreted neurotrophic factors, though in lower quantities compared with SLCs, and expressed glial markers p75 and GFAP even without stimulation	[128]
AT-MSCs (rat)	NeuraWrap™ sheath	15 mm gap in the rat sciatic nerve	Chemical and growth factors	4×10^6	Improvement in axonal regeneration and myelination. The conduits containing SLCs resulted in a 3.5-fold greater proportion of axons in the distal nerve stump compared with the empty conduits after 8 weeks	No undifferentiated MSC transplantation group	[129]
AT-MSCs (rat)	Silicone tube	7 mm gap in the rat facial nerve	Chemical and growth factors	1×10^5	Improvement in axonal regeneration and in the functional recovery of the facial nerve	AT-MSCs, SLCs, and SCs showed similar nerve regeneration potential after 13 weeks	[130]
AT-MSCs (ovine)	Acellular nerve allograft	30 mm gap in the ovine peroneal nerve	Chemical and growth factors	3×10^5	Improvement in hindlimb function, motor recovery, and remyelination	The autograft showed better organization of the myelin sheaths and axons than acellular nerve allografts recellularized with SLCs after 12 months	[131]
AT-MSCs (ovine)	Acellular xenografts (human)	20 mm gap in the ovine sciatic nerve	Chemical and growth factors	3×10^5	Improvement in metatarsus mobility and strength. Presence of several intrafascicular axons at the graft extremes	No difference was observed between the allograft and xenograft recellularized with SLCs groups in the biceps femoris and gastrocnemius electromyographic response after 6 months	[132]
BM-MSCs (rat)	Hollow fiber	12 mm gap in the rat sciatic nerve	Chemical and growth factors	$1-2 \times 10^7$	Motor nerve conduction velocity and sciatic nerve function improved significantly. There was an increase in the number of regenerated axons	No tumor formation was observed in the graft or the sciatic nerve segment after 6 months	[133]
BM-MSCs (human)	Transpermeable tube	10 mm gap in the rat sciatic nerve	Chemical and growth factors	$1-2 \times 10^7$	Increase in the number of regenerated axons and improvement in the sciatic function index	Intraperitoneal administration of FK506 as an immunosuppressant during the 3 weeks of evaluation	[134]
BM-MSCs (rat)	Chitosan conduit	12 mm gap in the rat sciatic nerve	Induction of neurospheres, exposure to growth factors, and co-culture	1.5×10^5	Enhanced axonal repair and remyelination	The nerve repair and functional recovery were similar to those from sciatic nerve-derived SCs	[135]
BM-MSCs (rabbit)	Autogenous vein	10 mm gap in the rabbit	Chemical and growth factors	2×10^5	Improvement in axon regeneration and remyelination	SLC group provided a faster rate of axonal extension and a larger area of myelination than	[136]

		facial nerve buccal branch				the BM-MSCs group
BM-MSCs (human)	Chitosan conduit	12 mm gap in the rat sciatic nerve	Induction of neurospheres, exposure to growth factors, and co-culture	1.5×10^5	Enhanced axonal regeneration and myelination	Subcutaneous administration of cyclosporin A for immunosuppression [137]
WJ-MSCs (human)	Transpermeable tube	8 mm gap in the rat sciatic nerve	Chemical and growth factors	$1-2 \times 10^7$	Improvement in axonal regeneration and functional recovery	No tumor formation was observed after 3 weeks. The ability of SLCs to promote axonal regeneration was similar to that of human SCs, as evidenced by functional recovery and histological evaluation. Subcutaneous administration of FK506 for immunosuppression [138]
UCB-MSCs (human)	3D-cell spheroids	Sciatic nerve crush in rats	Chemical and growth factors	5×10^5	Improvement in functional and structural recovery	Subcutaneous administration of cyclosporin A for immunosuppression [139]
GMSCs (human)	3D-collagen hydrogel	Sciatic nerve crush in rats	Encapsulation in the methacrylated 3D-collagen hydrogel	2×10^6	Improvement in axonal regeneration and functional recovery	SLCs demonstrated immunomodulatory activity, reducing M1 macrophage activation and promoting M2 macrophage polarization [120]

AT-MSCs: Adipose tissue-derived mesenchymal stem cells; BM-MSCs: Bone marrow-derived mesenchymal stem cells; GFAP: Glial fibrillary acidic protein; GMSCs: Gingiva-derived mesenchymal stem cells; MSC: Mesenchymal stem cell; SCs: Schwann cells; SLCs: Schwann-like cells; UCB-MSCs: Umbilical cord blood-derived mesenchymal stem cells; WJ-MSCs: Wharton's jelly-derived mesenchymal stem cells; 3D: Three-dimensional.

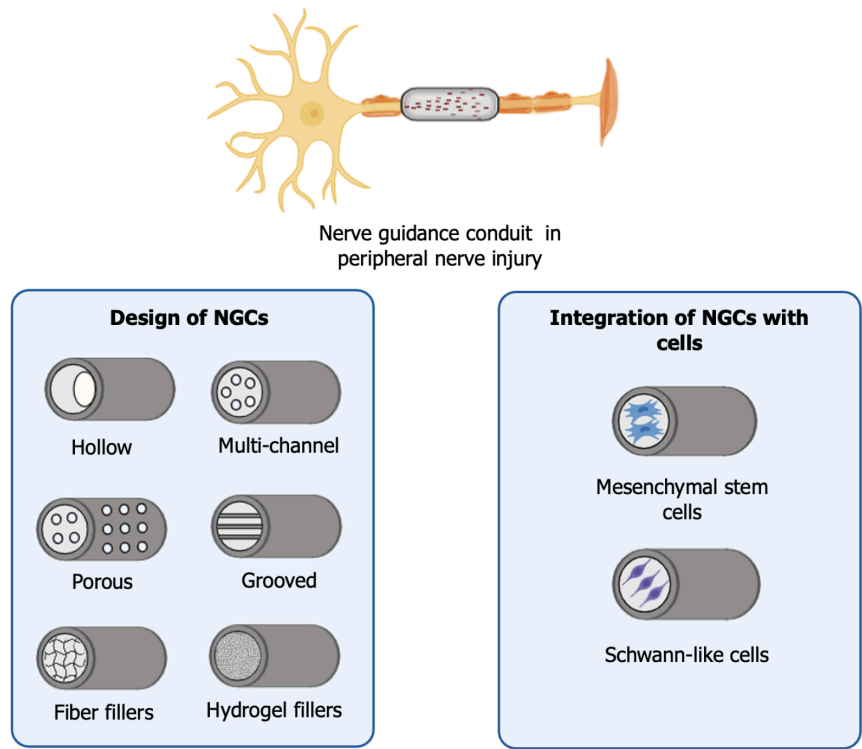


Figure 4 Summarized schematic of different designs to enhance nerve guidance conduits (NGCs). Design variations include hollow tubes, multichannel, porous, grooved structures, fiber, or hydrogel fillers. These designs can be used alone or in combination with mesenchymal stem cells or Schwann-like cells for the treatment of peripheral nerve injuries. NGCs: Nerve guidance conduits. Created in BioRender. Amorim, R. (2025) <https://BioRender.com/z6uzrjj>.

their clinical application for PNI treatment.

GENETIC ENGINEERING

Genetic engineering in MSCs has emerged as a promising tool to enhance their therapeutic properties through transfection with viral and non-viral vectors, enabling the targeted modification of their characteristics to meet specific needs[140]. This approach facilitates the insertion of therapeutic genes into MSCs, allowing their reprogramming to express or inhibit certain genes, overcoming limitations such as low concentration at the injury site and short survival time[44,54].

In the treatment of PNI, bone marrow MSCs from rats were transfected with BDNF and CNTF and combined with nerve transplantation to treat sciatic nerve injuries in rats, resulting in improved nerve function and increased myelin sheath thickness[141]. In another study, human bone marrow MSCs were transduced with lentivirus to overexpress VEGF, demonstrating positive effects both *in vitro* and *in vivo* in a murine sciatic nerve injury model[142]. This strategy promoted neurite outgrowth and maintained high VEGF expression for up to 14 days after transplantation[142]. Moreover, the addition of FGF-2 to rat adipose-derived MSCs, in combination with the overexpression of miR-218, showed potential to induce their transdifferentiation into the neural lineage *in vitro*[143]. Neuron-derived EVs have also been shown to play a key role in promoting neural differentiation of AT-MSCs, carrying synaptosomal-associated protein 25, miR-132, and miR-9[144]. Additionally, this process has demonstrated potential *in vivo*, where neuron-like cells derived from AT-MSCs helped reduce peripheral nerve degeneration after injury[144]. However, for clinical application, gene therapy still faces challenges such as the proper selection of target genes, maintaining stable expression in the patient, and ethical considerations[64].

LIMITATIONS AND CHALLENGES OF MSC-BASED THERAPIES FOR PNI

Despite promising results in preclinical studies, several limitations and challenges continue to impede the clinical translation of MSC-based therapies for PNI. A major concern is the inherent heterogeneity of MSC populations, which can vary according to tissue source, donor characteristics, and culture conditions. These variations can significantly influence their differentiation potential, immunomodulatory properties, and secretion of bioactive factors, including EVs, ultimately affecting therapeutic outcomes. Furthermore, MSC survival and integration within the injured nerve environment remain suboptimal, particularly in hostile microenvironments marked by inflammation and hypoxia. Another critical challenge is the absence of standardized protocols for MSC transplantation. Variability in cell dosage, delivery routes, and treatment timelines complicates inter-study comparisons and undermines the reproducibility and scalability of therapeutic approaches.

The long-term safety of MSC-based therapies also warrants further investigation. Potential tumorigenicity must be rigorously evaluated within standardized regulatory frameworks. While strategies such as genetic modification and transdifferentiation into SLCs have shown promise in enhancing the regenerative potential of MSCs, they introduce additional complexities related to safety, stability, and ethical considerations.

In parallel, the combination of MSCs with tissue-engineered scaffolds, such as NGCs, represents a promising avenue for promoting and directing nerve regeneration. However, for these constructs to achieve clinical relevance, they must demonstrate efficacy equal to or superior to autografts, the current gold standard for bridging long-gap nerve injuries. Continued efforts to optimize the design, biocompatibility, and functionalization of NGCs remain essential for improving functional outcomes and advancing clinical translation.

CONCLUSION

MSCs exhibit great therapeutic potential for the treatment of PNI, being effective in promoting immunomodulation, neuroprotection, and neuroregeneration. The combination of MSCs with NGCs emerges as a promising strategy to optimize nerve regeneration, providing structural support and promoting the guidance of axonal growth. This combined approach has shown significant benefits in preclinical models, accelerating the regeneration of damaged peripheral nerves. However, challenges remain, such as the proper integration of MSCs with NGCs and ensuring long-term stability.

Additionally, genetic engineering, the use of EVs, and the potential for MSCs transdifferentiation represent innovative pathways aimed at maximizing therapeutic outcomes. However, substantial challenges remain to be addressed, such as ensuring stable cell expression in the patient, the ethical issues involved, and the need for global consensus on the characterization of cells after transdifferentiation. Furthermore, it is essential to overcome difficulties related to large-scale production, ensuring quality and safety for clinical application.

Although significant progress has been made, further research is needed to overcome these barriers and establish MSC therapy as an effective reality for the clinical application of PNI. While MSC-based therapies have demonstrated promising preclinical results, their translation into routine clinical practice requires overcoming key challenges, including safety, scalability, and standardization. Addressing these limitations will be crucial to establish MSCs as a viable therapeutic option for PNI patients in the near future.

FOOTNOTES

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