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Contents

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EDITORIAL

ORIGINAL ARTICLE

Basic Study

SYSTEMATIC REVIEWS

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Contents

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EDITORIAL

Mesenchymal stem cells' "garbage bags" at work: Treating radial nerve injury with mesenchymal stem cell-derived exosomes

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Abstract

Unlike central nervous system injuries, peripheral nerve injuries (PNIs) are often characterized by more or less successful axonal regeneration. However, structural and functional recovery is a senile process involving multifaceted cellular and molecular processes. The contemporary treatment options are limited, with surgical intervention as the gold-standard method; however, each treatment option has its associated limitations, especially when the injury is severe with a large gap. Recent advancements in cell-based therapy and cell-free therapy approaches using stem cell-derived soluble and insoluble components of the cell secretome are fast-emerging therapeutic approaches to treating acute and chronic PNI. The recent pilot study is a leap forward in the field, which is expected to pave the way for more enormous, systematic, and well-designed clinical trials to assess the therapeutic efficacy of mesenchymal stem cell-derived exosomes as a bio-drug either alone or as part of a combinatorial approach, in an attempt synergize the best of novel treatment approaches to address the complexity of the neural repair and regeneration.

Key Words: Exosome; Mesenchymal stem cells; Nerve injury; Stem cells; Secretome; Regeneration

Core Tip: The extracellular vesicles constituting the insoluble component of the secretome were once considered cell's garbage bags. They have become a hot area of research since realizing their significance as an essential means of intracellular communication. They have shown promise for therapeutic applications for repairing and regenerating the damaged tissues *via* delivering their payload to the resident reparative cells and supporting them in the intrinsic repair process. Although stem cell-derived exosomes have been extensively studied for peripheral nerve injury repair in experimental animal models, their use for radial nerve injury repair in a patient, as the pilot study by Civelek *et al*, is expected to pave the way for assessment in future clinical trials.

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INTRODUCTION

Stem cells and their derived paracrine factors are potential therapeutic modalities to treat spinal cord injury, stroke, and neurodegenerative diseases[1]. Among different stem cell types, mesenchymal stem cells (MSCs) have remained at the forefront of characterization and assessment in the preclinical and clinical settings as choice cells for their regenerative properties in nerve injury repair[2]. They foster the survival and regeneration of neurons *via* multifaceted mechanisms that primarily include differentiation into morpho-functionally competent neural cells and the release of trophic factors, thereby establishing a conducive microenvironment for neural tissue repair[3]. Some of the latest published studies highlighting their findings in preclinical and clinical settings for peripheral nerve injury (PNI) treatment have been summarized in Tables 1 and 2[4-20].

Exosomes are small extracellular vesicles (50-100 nm in size bounded by a lipid bilayer membrane) released by cells as an integral part of their paracrine activity. They contain a specific cargo of bioactive molecules. Once considered the "garbage bags" for cell metabolic waste disposal[21], exosomes are being established as critical regulators of diverse physiological cell processes and essential mediators of intercellular communication[22,23].

MSC-derived exosomes exhibit neuroprotective and regenerative effects by modulating inflammation, promoting cell survival, antioxidant properties, anti-apoptotic and pro-proliferative activities, and stimulating neuronal differentiation [24]. They also have higher biocompatibility and low risk of tumorigenicity, microvascular, immune rejection, *etc.*; safety concerns are generally associated with using cell grafts[25]. As they copycat the regenerative effects of MSCs, they are potential candidates as the non-cellular alternatives for neurodegeneration. In the following sections, we will focus on advancements in PNI treatment using stem cells and their derived exosomes, recapitulated in Figure 1. Moreover, we will also delve into the clinical trials assessing stem cell-based and their derivative exosome-based approaches for treating PNI patients, with a critical appreciation of clinical experience in the pilot study published by Civelek *et al*[20] using MSCs-derived exosomes.

PNI AND INTRINSIC REPAIR PROCESS

Unlike the brain's synaptic plasticity, which allows it to have functional reorganization with limited or no repair or renewal in the event of injury[26], axonal regrowth through peripheral nerve sheaths has been observed in PNI as part of the recovery process[27,28] (Figure 2). However, the recovery process in PNI is influenced by the severity of the injury. In non-severe injuries, *i.e.*, neuropraxia and local demyelination, axonotmesis with intact neural stroma, and loss of funiculus and its contents, the nerve recovers from the damage by the inherent ability to repair[29].

On the contrary, injuries involving the severing of the nerve may require gold-standard surgical intervention. Diverse cellular and molecular events involving Schwann cells (SCs), macrophages, and extracellular matrix contribute to the repair process, which usually spans a prolonged duration[28]. Neuronal repair in the peripheral nervous system involves more than one mechanism, *i.e.*, axonal regrowth, central nerve cell restoration, and neurogenesis, to ensure functional recovery[30,31].

Axonal regrowth may involve damaged nerve cells from the peripheral ganglia or reactivation of signaling from the intact central nerve cells of the severed axons[32]. On the other hand, central nerve cell restoration involves sprouting, a process wherein new axons, dendrites, and synapses grow from the intact central nerve cell body. Neurogenesis, the growth of new neurons, is possible if the neurons retain some of their multipotent neural stem/progenitor cell population, especially near the injury site[33].

CELLULAR AND MOLECULAR BASIS OF PNI

SCs myelinate the peripheral axons, support the regrowth of axons by secreting laminin, fibronectin, and collagens, and

Table 1 Recently reported peripheral nerve injury repair in the experimental animal models

Ref.	Experimental model (*in vitro* or animal)	Therapeutic modalities	Main findings
MSCs-based therapy			
Zhang *et al*[4], 2024	SCs from injured sciatic nerves and HUVECs	MSCs treated with PRP-derived exosomes	Treatment with PRP-exosome improved MSC survival. Exosome-treated MSCs, co-cultured with SCs, reduced their apoptosis and enhanced SC proliferation after PNI. Similarly, exosome-treated MSCs also had pro-migratory and angiogenic effects. Cytokine array analysis and ELISA showed upregulation of 155 proteins and downregulation of six proteins, with many pro-angiogenic and neurotrophic factors. Western blot revealed the activation of the PI3K/Akt signaling pathway in exosomes-treated MSCs
Sivanarayanan *et al*[5], 2023	Sciatic nerve crush injury in rabbit	Allogenic BM-MSCs and their CM	BM-MSCs and BM-MSCS-CM treatment improved the regenerative capacity in acute and subacute injury groups, with slightly better improvements in the subacute groups. BM-MSCs supported the healing process of PNI, whereas CM increased the healing process
Yalçın *et al*[6], 2023	Sciatic nerve injury in rat	ADSCs	The study documented the role of syndecan-1 and heat shock protein 70 in the regenerative effects of ADSCs on PNI. Histology and EMG showed that treatment with ADSCs significantly improved nerve regeneration and its functionality *via* the release of nerve growth factor
Liu *et al*[7], 2020	Sprague-Dawley rats	SC-like ADSCs are placed on an acellular scaffold after treatment with nerve leachate	Sprague-Dawley rats were divided into four groups: Scaffold only, untreated ADSCs + scaffold, nerve leachate-treated ADSCs + scaffold, and autograft. Four months after treatment, the average area, density, and thickness of regenerated nerve fibers in the nerve leachate-treated ADSCs + scaffold group significantly increased compared to the untreated ADSCs + scaffold group. These data show the superiority of nerve leachate-treated ADSCs for treating PNI
Kizilay *et al*[8], 2017	Wistar rat model of sciatica nerve injury by clip compression	BM-MSCs	The proximal, distal, and mean latency values were higher in MSC treatment groups *vs* without MSC-treated animals. The nerve conduction velocity, compound action potential, and the number of axons in MSC-treated animals are higher than in non-MSC-treated animals. Also, myelin damage decreased in MSC-treated animals
Cell-free therapy			
Growth factor-based approach for PNI			
Shi *et al*[9], 2022	Rat sciatic nerve transection model		*In vitro* experimental studies show that BDNF/PLGA sustained-release microsphere treatment improved migration and neural differentiation of ADSCs. *In vivo* studies indicated that BDNF microsphere treatment significantly reduced the nerve conduction velocity compound amplitude compared to the untreated animals. Moreover, the BDNF microsphere group had more closely arranged and uniformly distributed nerve fibers than the control animals
Li *et al*[10], 2021	Rat sciatic nerve transection model	Leision site injection of a lentivirus expressing FGF13	FGF13 treatment successfully recovered motor and sensory functions *via* axon elongation and remyelination. FGF13 pretreatment enhanced SCs survival and increased cellular microtubule-associated proteins *in vitro* PNI model. The data supported the role of FGF13 in stabilizing cellular microtubules, which is essential for promoting PNI repair following PNI
Su *et al*[11], 2020	Rat sciatic nerve transection model	Composite nerve conduit with slow-release BDNF	The study used fabricated composite nerve conduits with slow-release BDNF to treat PNI and compare the regeneration potentials of autologous nerve grafts. The BDNF composite conduits remained bioactive for at least three months and successfully regenerated a 10-mm sciatic nerve gap
Lu *et al*[12], 2019	Rat model of sciatic crush injury	Intramuscular delivery of FGF21 once daily for seven days	FGF21 treatment led to functional and morphologic recovery with improved motor and sensory function, enhanced axonal remyelination and re-growth, and increased SC proliferation. Local FGF21 treatment reduced oxidative stress *via* activation of Nrf-2 and ERK. FGF21 also reduced autophagic cell death in SCs
Exosome-based approach for PNI			
Zhu *et al*[13], 2023	Mouse model of spared nerve injury	Exosomes from UC-MSCs under hypoxia	After 48 h of culture under 3% oxygen in a serum-free culture system, UC-MSCs secreted higher EVs than the control cells. SCs could uptake EVs *in vitro* and increase their growth and migration. The treatment of animals with EVs accelerated the recruitment of SCs at the PNI site and supported PN repair and regeneration
Hu *et al*[14], 2023	Rat model of the injured sciatic nerve	SCs-like cells derived from hA-MSCs. Exosomes from hA-MSCs or SC-like cells from hA-MSCs	SC-like cells were successfully differentiated from hA-MSCs and used for exosome collection. Treatment with exosomes from SC-like cells significantly enhanced (*vs* hA-MSCs-derived exosomes) motor function recovery, reduced gastrocnemius muscle atrophy, and supported axonal regrowth, myelin formation, and angiogenesis in the rat model. They were also more efficiently absorbed by SCs and promoted the proliferation and migration of SCs
Yin *et al*[15], 2021	*In vitro* model and a rat model of sciatic	ADSCs	Exosome treatment inhibited autophagy and karyopherin-α2 levels, which were significantly increased in SCs in the injured sciatic nerve, both *in vivo* and *in vitro*.

	nerve injury		Abrogation of karyopherin-α2 reduced SCs autophagy, with the role of miRNA-26b. Treatment with exosomes supported myelin sheath regeneration in rats with a sciatic NI
Liu *et al*[16], 2020	PNI model rats supported by *in vitro* studies	ADSCs and their derivative exosomes	Treatment with ADSC-derived exosomes significantly reduced SC apoptosis after PNI *via* increased Bcl-2 and decreased Bax mRNA expression, in addition to increasing SC proliferation. Histological data in PNI model rats also observed these effects
Chen *et al*[17], 2019	*In vitro* model and rat sciatic nerve transection model with a 10-mm gap	Human ADSCs-derived exosomes and *in vitro*	*In vitro* studies showed that SCs internalized human ASCs-derived exosomes to enhance their proliferation, migration, myelination, and secretion of neurotrophic factors. Treatment with ASC-exosomes supported axon regeneration in a rat sciatic nerve transection model with a 10-mm gap and supported myelination and restoration of denervation muscle atrophy. This data showed the efficacy of exosomes in promoting PN regeneration by restoring SC function
Masgutov *et al* [18], 2019	Wistar rat sciatic nerve injury model	ADSCs	ADSCs-derived MSCs were delivered using fibrin glue to the traumatic injury, helped to fix the cells at the graft site, and gave extracellular matrix support to the provided cells. The transplanted cells were neuroprotective on DRG L5 sensory neurons and stimulated axon growth and myelination. Also, MSCs promoted nerve angiogenesis and motor function recovery

ADSCs: Adipose-derived mesenchymal stem cells; BM-MSCs: Bone marrow-derived mesenchymal stem cells; BNDF: Brain-derived neurotrophic factor; EVs: Extracellular vesicles; hA-MSCs: Human amniotic-derived mesenchymal stem cells; HUVEC: Human umbilical vein endothelial cells; CM: Conditioned medium; EMG: Electromyography; ERK: Extracellular regulated protein kinases; FGF: Fibroblast growth factor; MSCs: Mesenchymal stem cells; Nrf-2: Nuclear factor erythroid-2-related factor 2; PN: Peripheral nerve; PNI: Peripheral nerve injury; PLGA: Poly(D, L-lactide-co-glycolide; PRP: Platelet-rich plasma; SCs: Schwan cells; UC-MSCs: Umbilical cord mesenchymal stem cells; PI3K: Phosphoinositide 3-kinase.

produce neurotrophic factors, *i.e.*, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor. Additionally, they facilitate remyelination by aligning as Bands of Büngner, clear cellular and myelin debris by phagocytosis, and guide proper axonal regeneration by increasing cell adhesion molecules NCAM, L1, and N-cadherin and early re-expression of bHLH family transcription factors protein growth-associated protein-43, and that helps actin and microtubule cytoskeletal recovery[34]. SCs and fibroblasts also secrete endoneurial matrix comprising various components, *i.e.*, collagen, glycoproteins (fibronectins, laminins), glycosaminoglycans, and proteoglycans[35]. These matrix components can inhibit or stimulate axonal repair, and their activity is enhanced during axonal repair after injury.

Joining hands with SCs are macrophages, especially M2 macrophages, that remove the debris from the damaged peripheral nerves. Additionally, they provide a conducive microenvironment for nerve repair and growth *via* modulating inflammation and by releasing pro-inflammatory cytokines, *i.e.*, interleukin (IL)-1 and tumor necrosis factor-α, to promote SC activation[7]. During the resolution phase of PNI repair, the macrophages also stimulate the release of anti-inflammatory cytokines, *i.e.*, IL-10, to help resolve inflammation and promote tissue healing.

TREATMENT ADVANCES FOR PNI

PNI can result in significant functional impairments, necessitating proper therapeutic options for nerve repair. In clinical settings, microsurgical intervention by nerve autografting is considered the gold-standard treatment for PNI. However, it is limited by the availability of the nerve graft, chances of infection, and neuroma development. The other contemporary treatment options for PNI include direct suturing, SCs transplantation, and electrical stimulation, but with their respective deficiencies, especially when treating significant nerve defects wherein they fail to achieve complete repair. The following section elaborates on the current advancements in PNI treatment using cell-based and cell-free approaches, as summarized in Figure 2[36].

MSCs AND PNI REPAIR

The cell-based therapy approach has come a long way with encouraging data for peripheral nerve repair and regeneration; several stem/progenitor cells have been assessed for their neuronal reparability in pre-clinical models. These include pluripotent cells, *i.e.*, embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult tissue-derived stem/progenitor cells, *i.e.*, MSCs, neural stem cells (NSCs), *etc.* Although pluripotent stem cells have high differentiation potential, using ESCs has ethical issues and moral strings attached. In contrast, using iPSCs (considered surrogate ESCs) has tumorigenic potential due to genomic instability induced during reprogramming[37]. MSCs from amongst the adult tissue-derived stem cells have gained considerable attention in nerve regeneration studies in experimental animal models with their self-renewal, robust nature, excellent cell biology, and multipotentiality[38]. Table 1 summarizes the data published by various recently published experimental animal studies using MSCs. From the different tissue sources of MSCs, adipose tissue-derived MSCs and bone marrow (BM)-derived MSCs have shown excellent neural regeneration and repairability. Their reparability is *via* multifactorial mechanisms encompassing neuroprotection to differentiation to adopt morphofunctional competent neural cells besides the release of secretome

Table 2 Clinical studies for peripheral nerve injury repair using Schwan cells, stem cells, and their derived exosomes

NCT#	Study title	Conditions	Interventions	Primary outcome	Sponsor	Collaborators
NCT04346680	Intraoperative ADSC administration during nerve release	Neurotmesis of peripheral nerve disorder	ADSC administration	Electrophysiological improvement, improvement in EMG - the appearance of activities in denervated muscles, one year	Mossakowski MRC Polish Academy of Sciences	Centre of Postgraduate Medical Education
NCT03964129	BMAC nerve allograft study	PNI upper limb	Avance nerve graft with autologous BMAC	Comparison of AEs between patients treated with ANG with BMAC and the historical data of nerve repairs with the ANG only. Long-term study - AEs, such as infection, wound dehiscence, neuropathy, carpal tunnel syndrome, bleeding, seroma, and lymphocele, will be recorded and analyzed. AEs will be mapped to a MedDRA-preferred term and system organ classification	Brooke Army Medical Center	Walter Reed National Military Medical Center; Cleveland Clinic Lerner Research Institute
NCT03359330; PKUPH-PNI	Mid-term effect observation of biodegradable conduit small gap tublization repairing PNI	PNIs	Degradable conduit small gap tublization	To observe the mid-term clinical effect of biodegradable conduit small gap tublization on the repair of PNI in multi-center patients and fresh PNIs in the upper extremities	Peking University People's Hospital	-
NCT05541250	Safety and efficacy of autologous human SCs augmentation in severe peripheral nerve injury	PNIs	Autologous human SC	The primary purpose of this phase I study is to evaluate the safety of injecting one's SCs along with nerve auto-graft after a severe nerve injury, such as a sciatic nerve or brachial plexus injury	University of Miami, Florida, United States (Recruiting)	-
NCT04654286	Clinical outcomes of HAM and allogeneic MSCs composite augmentation for nerve transfer procedure in brachial plexus injury patients	Brachial plexus neuropathies	Nerve transfer or nerve transfer with HAM-MSC composite wrapping	AROM pre-surgery and 12-month follow-up for shoulder flexion, extension, abduction, adduction, external rotation, and internal rotation using the MRC scale (ranging from 0-5)	Dr. Soetomo General Hospital, Jakarta	
Huang *et al*[19], 2016	A clinical study on the treatment of peripheral nerve injury growth factor of mecobalamin combined with nerve	150 PNI patients	Mecobalamin (0.5 mg, I.V, once a day) combined with NGF (30 mg, I.M injection, once a day) for 3-6 wk	Treatment with mecobalamin combined with NGF improved the sensor-imotor evaluation of the curative effect made by the British Medical Research Institute of Neurotrauma Society	Guangxi Basic Science and Technology Plan Project PR China (No.: 20111209)	
Civelek *et al* [20], 2024	Effects of exosomes from mesenchymal stem cells on functional recovery of a patient with total radial nerve injury: A pilot study	One patient with total radial nerve injury	WJ-MSCs derived exosomes	The six-month follow-up based on the BMRC and Mackinnon-Dellon scales showed improved motor (M5, excellent), and sensory functions also showed improvement (S3+, good). These results were achieved without physical therapy. Substantial axonal damage was observed at a ten-week follow-up, but nerve re-innervation was observed by EMG, which also improved significantly during the six-month follow-up	Department of Neurosurgery, University of Health Sciences	

ADSCs: Adipose tissue-derived mesenchymal stem cells; AEs: Adverse effects; ANG: Avance nerve graft; AROM: Active range of motion; HAM-MSC: Human amniotic membrane-derived mesenchymal stem cells; BMAC: Bone marrow aspirate concentrate; EMG: Electromyography; MRC: Medical Research Council; MSCs: Mesenchymal stem cells; SCs: Schwan cells; PNI: Peripheral nerve injury; WJ-MSCs: Wharton jelly-derived mesenchymal stem cells; NGF: Nerve growth factor; BMRC: Behavioral Medicine Research Council; ADSC: Adipose-derived stem cell.

containing neurotrophic factors and exosomes rich in the bioactive payload of microRNAs (miRNAs), enzymes, and protein[39], which will be discussed in the following sections. To enhance their stemness and reparability, they have been combined with NSCs, preconditioned to enhance their paracrine activity, or genetically modified to serve as a source of neurotrophic factors as paracrine factors[40,41].

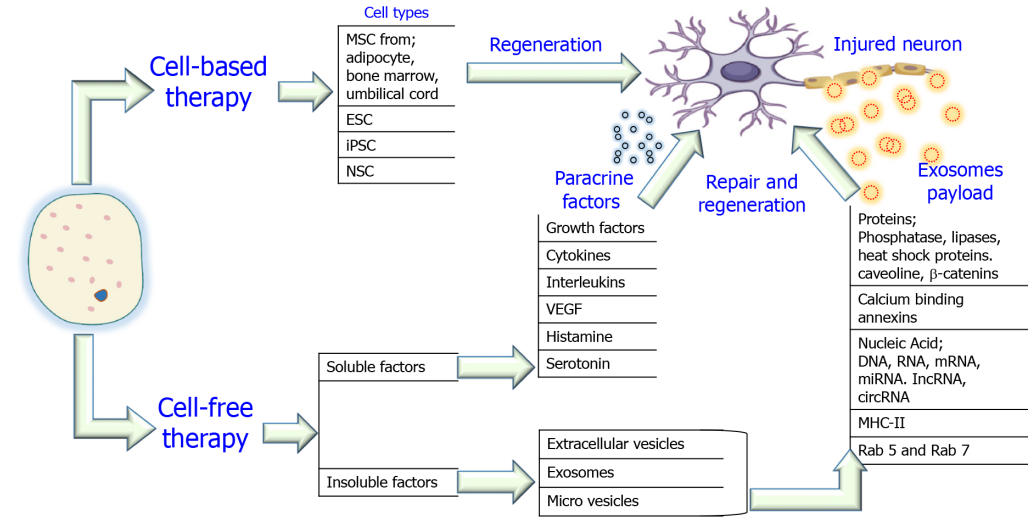

Figure 1 The novel cell-based and cell-free therapy approaches for peripheral nerve injury repair and regeneration. MSC: Mesenchymal stem cell; iPSC: Induced pluripotent stem cell; NSC: Neural stem cell; VEGF: Vascular endothelial growth factor; miRNA: MicroRNA; lncRNA: Long non-coding RNA; circRNA: Circular RNA; MHC: Major histocompatibility complex.

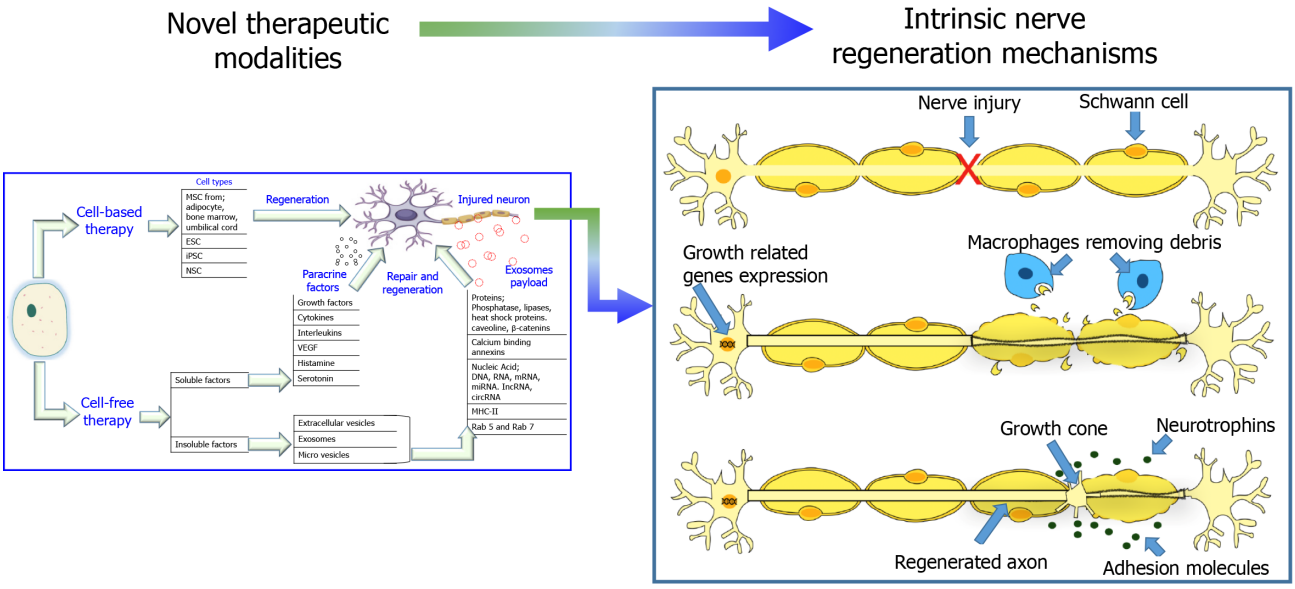

Figure 2 Summary of the intrinsic peripheral nerve injury repair mechanisms and the emerging novel treatment modalities to support intrinsic peripheral nerve injury repair. MSC: Mesenchymal stem cell; iPSC: Induced pluripotent stem cell; NSC: Neural stem cell; VEGF: Vascular endothelial growth factor; miRNA: MicroRNA; lncRNA: Long non-coding RNA; circRNA: Circular RNA; MHC: Major histocompatibility complex.

MSCs have also advanced to the clinical assessment for PNI repair in different clinical studies (Table 2), mainly as an adjunct to other therapeutic interventions, such as intraoperative administration (Clinicaltrials.org ID: NCT04346680), being part of the nerve transfer composite (Clinicaltrials.org ID: NCT04654286), or avance nerve transfer (Clinicaltrials.org ID: NCT03964129).

CELL-FREE THERAPY-BASED APPROACHES FOR PNI REPAIR

Growth factor-based strategy

Besides cell-based therapy, there has been immense interest in using a growth factors-based approach to support neuronal regeneration and functional recovery[42]. Several growth factors have been identified as potential candidates for this end (Table 3). These growth factors contribute *via* interacting with each other to initiate various signaling pathways to guide and stimulate regeneration and functional recovery of the injured neurons. A generally accepted mechanism of growth factor-based treatment of PNI is that the target-derived growth factors are captured at the nerve

Table 3 List some commonly studied growth factors for peripheral nerve injury treatment

Ref.	Growth factor
Sandoval-Castellanos *et al*[43], 2020	Brain-derived neurotrophic factor
Xu *et al*[44], 2023	Ciliary neurotrophic factor
Gu *et al*[45], 2024	Chemokine platelet factor-4
Romano and Bucci[46], 2020	Epidermal growth factor
Cintron-Colon *et al*[47], 2022	Glial cell line-derived neurotrophic factor
Ye *et al*[48], 2022	Hepatocyte growth factor
Slavin *et al*[49], 2021	Insulin-like growth factor-1
Alastra *et al*[50], 2021	Nerve growth factor
Li *et al*[51], 2023	NGF+ basic fibroblast growth factor
Golzadeh and Mohammadi[52], 2016	Platelet-derived growth factor
Ding *et al*[53], 2024	Transforming growth factor
Xu *et al*[44], 2023	Vascular endothelial growth factor

NGF: Nerve growth factor.

terminals *via* receptor-mediated endocytosis and get retrogradely transported to cell bodies to impart their neurotrophic action.

From the list, neurotrophic growth factors families and cytokines, *i.e.*, NGF, GDN, fibroblast growth factor (FGF), ciliary neurotrophic factor, *etc.*, are critical in oligodendrocyte precursors' migration, proliferation, and differentiation and regulate axonal interactions and myelination. Some reported signaling pathways underlying these cellular level changes include the mitogen-activated protein kinase, phosphoinositide 3-kinase/Akt, nuclear transcription factor-kappa B, BDNF/Trk, Ras/extracellular regulated protein kinases, and transforming growth factor-β[54]. Understanding their interaction with specific receptors and the downstream signaling is essential for progressing growth factor-based therapeutic intervention. Numerous preclinical and clinical studies have investigated the efficacy of growth factor-based therapies in promoting nerve regeneration in animal models with PNI, as summarized in Tables 1 and 2.

MSC-derived exosomes for PNI

As discussed earlier, the MSCs-based cell therapy approach has shown promise in PNI treatment. Still, their use is not without limitations, *i.e.*, tumorigenesis, triggering an immune response, rejection of the cell graft, off-the-shelf non-availability, logistic issues, *etc.*, hampered the pace of their reckoning as a routine treatment option[55,56]. Hence, exosomes derived from different cell types, *i.e.*, SCs, MSCs, *etc.*, offer potential alternatives to overcome these limitations [57]. Their physiological functions primarily involve long-distance intracellular communication, using their surface proteins and lipid rafts to fuse with the recipient cells and deliver the payload of bioactive molecules. Alternatively, they can be taken up by the recipient cells *via* endocytosis.

An essential phase in exosome biogenesis is the initiation of intraluminal vesicles (ILVs) through the invagination of the endosomal membrane[58,59]. This is followed by payload encapsulation consisting of proteins, lipids, mRNA, miRNA, long non-coding RNA (lncRNA), circular RNAs (circRNAs), DNA, enzymes, signaling proteins, sphingolipids, *etc.*, and the release of ILVs into the extracellular environment as exosomes[60,61]. Each cell type's payload composition is distinct under a given set of conditions[62,63], contributing to their functional heterogeneity, *i.e.*, cell survival, apoptosis, proliferation, immunomodulation, *etc.* More recently, exosome modification protocols are being developed to modulate them for good biocompatibility, low immunogenicity, capability to cross biological membrane barriers, and, more importantly, to carry a specific payload composition of interest. Different exosome modification techniques are summarized in Figure 3. In line with their diverse theragnostic applications, MSCs-derived exosomes have been extensively studied to support neuronal functional recovery and regeneration in PNI experimental animal models[14,17,64].

The treatment of SCs with MSCs-derived exosomes reduces their autophagy *via* miRNA-26b mediated abrogation of karyopherin subunit α2[15], improves SC proliferation dose-dependently, entering SCs through endocytosis to modulate their gene expression profile and supporting their re-myelination[15,17,65,66]. Exosome-based treatment also exerts neuroprotective effects *via* PI3/Akt signaling activation[67]. Currently, "smart exosomes" are being developed by reprogramming and modulating their surface characteristics for efficient, targeted uptake by the recipient cells and manipulating their payload for delivery to the recipient cells[68]. For example, one of the essential entities in the payload are miRNAs, small, ncRNA molecules with mega functions as cell function regulators[69], that get delivered to the injured neurons during cellular communication[64,70]. They affect neuron differentiation, proliferation, angiogenesis, axonal regrowth, and other cellular functions[71]. For example, MSCs' exosome-derived miR-21, miR-124, and miR-133 have been attributed to promoting neuronal regeneration[72].

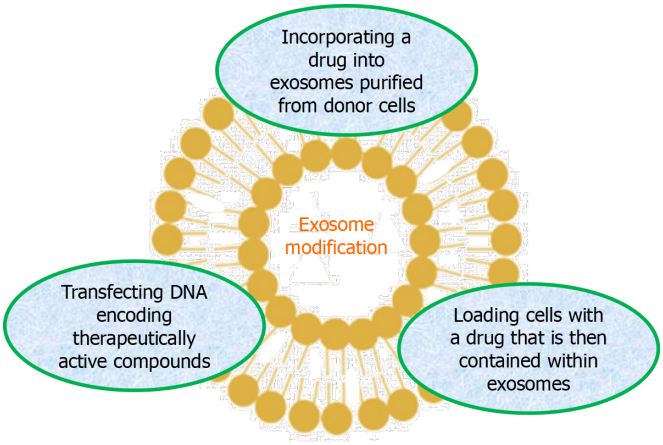

Figure 3 Payload manipulation of mesenchymal stem cells-derived exosomes.

In the neural injury model, MSCs-derived exosomes overexpressing miRNA-133b transferred miRNA-133b to injured neuronal cells, promoting post-stroke neuronal remodeling and functional recovery[73]. Furthermore, MSC exosomes have demonstrated benefits in brain injury, accelerating recovery through neurosynaptic remodeling, neurogenesis, and angiogenesis[74]. Besides miRNAs, circRNAs are resistant to degradation, act as miRNA sponges in neural apoptosis, angiogenesis, and synaptic plasticity modulation, and hold immense promise for neuroregeneration[75]. MSC-derived exosomal lncRNAs have been reported to enhance neuronal survival and promote axonal regeneration after nerve injury. Notably, lncRNA HOTAIR and MALAT1 have shown significant potential in promoting neuroregeneration by modulating several molecular pathways involved in nerve repair.

MSCS AND THEIR EXOSOMES FOR PNI IN CLINICAL SETTINGS

PNI, arising from a diverse range of etiologies such as trauma and underlying medical conditions, poses substantial challenges in both clinical management and subsequent restoration of functional capacity. MSC-derived exosomes, assessed in clinical settings for treating various disease conditions[76,77], have also progressed to clinical application for treating PNI as a part of the cell-free therapy approach. There are at least five registered clinical trials for the safety and efficacy assessment of SCs, MSCs, and their derived exosomes, although their current status remains unknown (Table 2). MSCs focus on diverse tissue sources, *i.e.*, adipose tissue, BM, and human amniotic membrane (HAM), due to their superior biology, paracrine activity, and differentiation characteristics[78].

Mossakowski Medical Research Council Polish Academy of Sciences has registered a clinical trial entitled "Intraoperative ADSCs Administration During Nerve Release" (ClinicalTrials.gov Identifier: NCT04346680). The trial proposes autologous adipose-derived stem cell (ADSC) transplantation in six patients with failure to reconstruct peripheral nerves. ADSCs will be delivered during a last-chance surgery (neurolysis and nerve release) on a previously reconstructed nerve. The patients included in the study will be subjected to clinical and electrophysiological assessment. The patients will receive ten microinjections of ADSC along the injured nerve, and safety, adverse events, and efficacy, *i.e.*, electromyography (EMG) and sensory threshold, will be assessed. On the other hand, the second registered study, "BMAC Nerve Allograft Study" (ClinicalTrials.gov Identifier: NCT04346680), will adopt a combinatorial approach involving an avance nerve graft combined with BM aspirate concentrate delivery. The third study, "Clinical Outcomes of Human Amniotic Membrane and Allogeneic Mesenchymal Stem Cells Composite Augmentation for Nerve Transfer Procedure in Brachial Plexus Injury Patients" (ClinicalTrials.gov Identifier: NCT04654286), will investigate the safety and efficacy of a composite between HAM and allogeneic ADSCs as a wrapping in the nerve transfer procedure of upper traumatic brachial plexus injury patients, with a focus on the augmentation of axonal regeneration. Another phase I study is entitled "Safety and Efficacy of Autologous Human SCs Augmentation in Severe Peripheral Nerve Injury" (NCT05541250) at the University of Miami, United States. The study, with primary safety and efficacy endpoints, is still in the recruitment stage.

Unlike the aforementioned clinical trials, pilot study data reported by Civelek *et al*[20] is unique in using MSCs-derived exosomes for therapeutic intervention as part of the cell-free therapy approach. The authors rationalized using exosomes and anticipated that exosomes would deliver their miRNA payload to the injured nerve, leading to the repair and regeneration of the nerve and reducing the inflammatory activity in the injured area *via* anti-inflammatory cytokines. The authors used 1 mL exosomes divided into four doses, with 1.25 billion vesicles each, delivered epineurally, after using a sural autograft. Functional sensory and motor recovery were observed as early as the 10th-wk post-grafting, and indications of re-innervation were evidenced by neurological examination and control EMG during a six-month follow-up. These data enhance our understanding of the neurobiological consequences of peripheral nerve damage and emphasize the potential of MSC-derived exosomes, offering avenues for future clinical advancements. Despite encouraging data from the study, it has its limitations. Firstly, it is a pilot study that includes only one patient. Hence, the data needs to reflect the safety and efficacy of the treatment approach, which necessitates more extensive studies

involving more participants with a control arm for comparison. Besides, the rationale for exosome dose selection has little justification. There has yet to be an attempt to profile the exosome payload composition, *i.e.*, miRNA, cytokines, growth factors, *etc*. The authors, therefore, assumed that specific miRNAs might have participated merely based on the published data. These limitations certainly make it challenging to comprehend the underlying mechanism. Nevertheless, despite these limitations, the study is a leap forward in neural repair and regeneration.

CONCLUSION

In conclusion, the recent advances in cell-based (especially MSC- and its derived exosomes) have shown promise in both preclinical and clinical settings; however, the field is still evolving and needs further research before it can be adopted as a routine therapeutic modality for PNI repair and neural regeneration. The pilot trial report from Civelek *et al*[20] is a leap forward in the clinical arena that has already started evolving but warrants a more extensive, systematic, and well-defined study. A few challenges encountered in using exosomes in neural repair and regeneration necessitating particular focus include optimizing an efficient isolation and purification protocol for clinical-grade exosome preparation, a method to achieve a well-defined payload of exosomes, and an optimal exosome delivery method for treating PNI. Given the complexity of an injured nerve's repair and regeneration process, it would be prudent to adopt a combinatorial approach by combining exosome delivery with other emerging PNI treatment approaches. For example, it can be integrated with the nanoparticle-based approach, which gives encouraging results in promoting peripheral nerve repair and neuroprotection, besides efficient drug delivery methods[79]. On the same note, synergizing the therapeutic potential of exosomes as a bio-drug with other treatment approaches, including surgical end-to-end anastomoses, is worth exploiting for optimal therapeutic benefits.

FOOTNOTES

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