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MINIREVIEWS

Bone marrow mesenchymal stem cells in treatment of peripheral nerve injury

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Abstract

Peripheral nerve injury (PNI) is a common neurological disorder and complete functional recovery is difficult to achieve. In recent years, bone marrow mesenchymal stem cells (BMSCs) have emerged as ideal seed cells for PNI treatment due to their strong differentiation potential and autologous transplantation ability. This review aims to summarize the molecular mechanisms by which BMSCs mediate nerve repair in PNI. The key mechanisms discussed include the differentiation of BMSCs into multiple types of nerve cells to promote repair of nerve injury. BMSCs also create a microenvironment suitable for neuronal survival and regeneration through the secretion of neurotrophic factors, extracellular matrix molecules, and adhesion molecules. Additionally, BMSCs release pro-angiogenic factors to promote the formation of new blood vessels. They modulate cytokine expression and regulate macrophage polarization, leading to immunomodulation. Furthermore, BMSCs synthesize and release proteins related to myelin sheath formation and axonal regeneration, thereby promoting neuronal repair and regeneration. Moreover, this review explores methods of applying BMSCs in PNI treatment, including direct cell transplantation into the injured neural tissue, implantation of BMSCs into nerve conduits providing support, and the application of genetically modified BMSCs, among others. These findings confirm the potential of BMSCs in treating PNI. However, with the development of this field, it is crucial to address issues related to BMSC therapy, including establishing standards for extracting, identifying, and cultivating BMSCs, as well as selecting application methods for BMSCs in PNI such as direct transplantation, tissue engineering, and genetic engineering. Addressing these issues will help translate current preclinical research results into clinical practice, providing new and effective treatment strategies for patients

with PNI.

Key Words: Bone marrow mesenchymal stem cells; Peripheral nerve injury; Schwann cells; Myelin sheath; Tissue engineering

Core Tip: Bone marrow mesenchymal stem cells (BMSCs) have become ideal seed cells for the treatment of peripheral nerve injury (PNI) due to their strong differentiation potential and the possibility of autologous transplantation. In this review, we introduce the biological characteristics of BMSCs related to PNI, outline the current mechanisms by which BMSCs promote the regeneration and repair of PNI, and summarize the various application methods of BMSCs in PNI, confirming the potential of BMSCs in the treatment of PNI and providing great support for the development of new treatment strategies for nerve regeneration and repair in PNI.

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INTRODUCTION

Peripheral nerve injury (PNI) refers to damage that occurs to the peripheral nerve trunk or its branches due to direct or indirect trauma from external sources. It is characterized by sensory, motor, and autonomic dysfunction in the trunk or limbs, representing one of common neurological disorders in clinical practice[1]. PNI is a global issue, with an annual incidence rate of approximately 13/100000 to 23/100000 in developed countries[2-5]. While peripheral nerve axons can regenerate after injury, achieving complete functional recovery is often challenging in cases of proximal nerve injuries or large nerve defects[6]. Currently, autologous nerve transplantation is considered the gold standard for PNI repair[7]. However, even under ideal conditions, this approach does not fully restore impaired motor and sensory functions[8]. Additionally, it has significant drawbacks, such as prolonged surgical time, high economic costs, insufficient donor areas for reconstruction of long or multiple nerve defects, and potential donor site damage (painful neuroma, scarring, and sensory deficits)[9]. In recent years, several new methods for PNI repair have emerged, showing positive effects on restoring the continuity of injured neuroanatomy. However, their ability to restore nerve function is not ideal, and they all have varying degrees of limitations[10].

Tissue engineering is an emerging discipline in the field of biotechnology and has gained significant attention in PNI research. Previous studies have demonstrated that transplantation of Schwann cells (SCs) can promote nerve regeneration and accelerate nerve function recovery[11]. However, obtaining a large number of SCs in a short period is challenging, and it may cause irreversible damage to the donor area, thus limiting the clinical application of SCs transplantation[12]. Recent research has found that adult mesenchymal stem cells (MSCs) can also promote nerve regeneration and show potential for treating PNI, making them a more ideal alternative to SCs. Bone marrow MSCs (BMSCs) are one type of adult MSC with strong differentiation potential and advantages in autologous transplantation. Numerous studies have indicated that BMSCs can differentiate into nerve-like cells during the PNI treatment process and play a crucial role in nerve growth factor (NGF) secretion, endogenous stem cell migration and differentiation, and neovascularization[13-15]. These findings suggest that BMSCs effectively promote the repair of neurological deficits, which makes them ideal seed cells for PNI repair. Researchers are also striving to translate preclinical research findings into practical clinical applications for PNI patients. BMSCs can be applied to PNI therapy through a variety of techniques, such as cell transplantation, tissue engineering, gene engineering, and cell therapy, including the use of BMSC-derived exosomes. These approaches have the potential to improve the effectiveness of PNI regeneration and offer new hope for PNI patients.

Through literature search and analysis (Figure 1), in this review, we present the biological properties of BMSCs associated with PNI. We summarize the current mechanisms by which BMSCs promote nerve regeneration and repair in PNI, as well as various application methods in PNI. Moreover, based on these findings, we identify the existing problems and limitations in order to deepen our understanding of BMSCs, optimize treatment strategies, address their shortcomings in clinical application in PNI, and promote their use in PNI clinical practice.

BIOLOGICAL PROPERTIES OF BMSCS IN TREATMENT OF PNI

BMSCs are a type of pluripotent stem cell that, under specific conditions, can differentiate not only into tissue cells from the mesodermal lineage, such as osteocytes, chondrocytes, and cardiomyocytes[16,17], but also undergo transdifferentiation across germ layers to form neurons, glial-like cells from the ectoderm, and hepatocytes, among others[18]. Silva *et al*[19] discovered that BMSCs express genes associated with both epithelial tissues and mesenchymal tissues, providing a

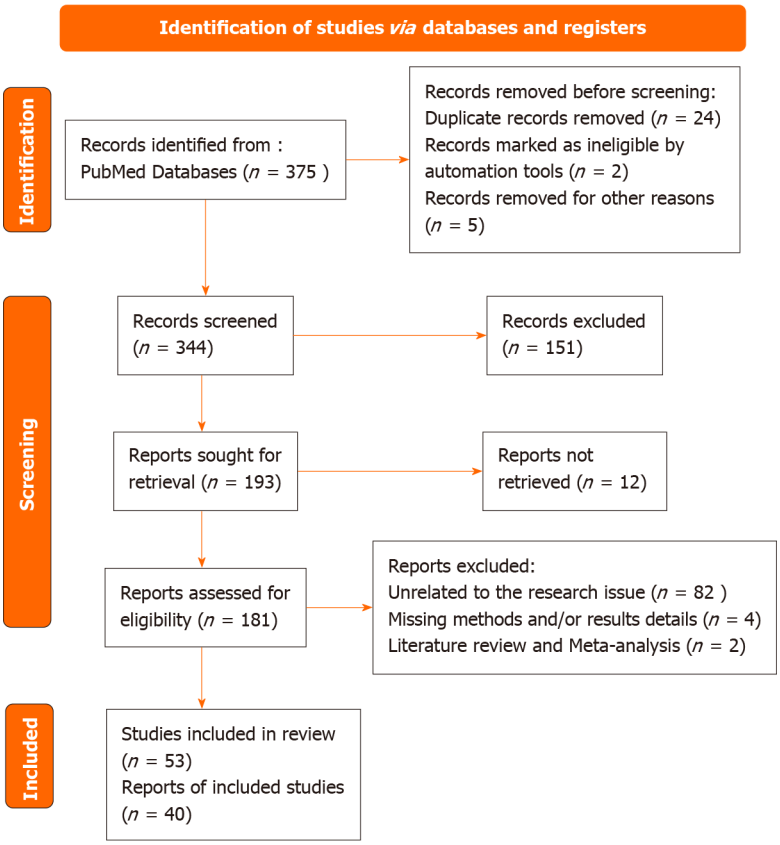

Figure 1 Flow chart of literature search and selection criteria. The initial search resulted in 344 articles. Out of 344 full-texts assessed, 251 articles were excluded. Thus, 93 articles that met the eligibility criteria were included.

theoretical basis for their multi-lineage differentiation potential at the gene level. Additionally, BMSCs possess self-renewal capacity. Tamir *et al*[20] found that approximately 90% of BMSCs are in the G0/G1 phase, which confirms their robust self-renewal capabilities.

BMSCs have no specific surface markers and generally exhibit low expression of major histocompatibility complex (MHC)-I molecules and do not express MHC-II molecules. They also do not express molecules required for T lymphocyte activation, such as Fas ligand and co-stimulatory molecules like B7-1, B7-2, and CD40 L[21]. This characteristic gives BMSCs low immunogenicity and strong immune-suppressive properties. Therefore, studies have shown that when co-cultured with allogeneic and xenogeneic T lymphocytes, BMSCs do not induce significant T cell proliferation but rather inhibit T cell proliferation[22]. In addition to being non-immunogenic, BMSCs are not targeted by CD8+ T cells, which allows them to evade cytotoxic T cell and natural killer cell killing, making them beneficial for successful autologous and allogeneic transplantations[23]. Furthermore, the antigenicity of BMSCs does not increase with their differentiation[24].

Indeed, it is evident that BMSCs possess the potential for multi-lineage differentiation and robust self-renewal capacity. Moreover, when transplanted into the body, they do not trigger significant rejection responses and can be allografted without causing immune rejection reactions[25,26]. The fact that BMSCs do not require the use of immunosuppressive drugs further adds to their appeal as seed cells for treating PNI, making them a promising candidate for potential applications in PNI therapy.

MECHANISMS OF BMSCS IN TREATMENT OF PNI

After PNI, if neurons have not died, their axons can undergo regeneration. SCs play a critical role in the repair of the peripheral nervous system. Following Wallerian degeneration of the peripheral nerve, SCs rapidly and massively proliferate, forming Büngner bands. They are involved not only in the formation, synthesis, and secretion of various NGFs but also in the synthesis and secretion of various extracellular matrix (ECM) components and other cell adhesion molecules. The above-mentioned NGFs, ECM, and cell adhesion molecules form gaps or tight junctions with adjacent axons, creating direct channels for the transfer of small molecules and information. These play an essential role in nerve injury regeneration and repair. Under specific conditions, BMSCs can differentiate into neural cells, including SC-like cells, and exert corresponding effects. In this section, we will explore the various functions of BMSCs in PNI repair and list the involved molecular mechanisms.

Differentiation into neural cells

BMSCs are one of the most widely used sources of cells for nerve regeneration. After transplantation, they can differentiate into different cells, such as neurons, astrocytes, and SC-like cells, under the influence of different physiological microenvironments and express corresponding antigen markers. *In vitro* studies have found that BMSCs can be induced to differentiate into neural-like cells by antioxidants (such as dimethyl sulfoxide and β-mercaptoethanol), cytokines [retinoic acid, basic fibroblast growth factor (bFGF), and epidermal growth factor], traditional Chinese medicine preparations (tetramethylpyrazine and baicalin), gene transfection, and other methods[27,28]. However, whether these induced neural-like cells possess the functional characteristics of normal neurons remains controversial. For instance, Hofstetter *et al*[29] successfully induced rat BMSCs to differentiate into neural cells using butylated hydroxyanisole but did not record the electrophysiological activity of mature neuronal cells. Some researchers believe that this phenomenon is not related to cell differentiation but rather cytotoxic changes[27]. On the other hand, other studies have shown successful induction of rat BMSCs into neural-like cells using a combination of bFGF, dimethyl sulfoxide, and butylated hydroxyanisole, with the capture of excitatory electrophysiological characteristics[27,28]. Wislet-Gendebien *et al*[30], through co-culturing, induced rat BMSCs to differentiate into neural cells that produced single action potentials and responded to neurotransmitters such as γ-aminobutyric acid, glycine, and glutamate. These findings suggest that BMSCs can differentiate into excitable neural-like cells *in vitro*.

In *in vivo* studies, Cuevas *et al*[31] injected 50000 bone MSCs (pre-labelled with bromodeoxyuridine BrdU) in 5 μL of culture medium solution into the distal stump of transected sciatic nerve of the rats, and found that after 33 d of implantation, almost 5% of BrdU cells express Schwann cell-like phenotype. Dezawa *et al*[32] obtained GFP-expressing BMSCs (GFP-MSCs) by retroviral vectors, adjusted the concentration of GFP-MSCs to (1-2) × 10^7 cells/mL, and then injected them into hollow fibres to make an artificial graft. The artificial graft was anastomosed to the cut end of the proximal nerve segment of the sciatic nerve in rats, and a large number of newly formed fibers were observed after 3 wk. They found that BMSCs had a myelination effect in regenerating nerve fibers through immunoelectron microscopy and confocal microscopy, indicating that BMSCs can differentiate into neuron-like cells and secrete a large amount of NGFs to induce axon growth. Additionally, BMSCs can directly transform into SCs to repair injured nerves, which has attracted considerable attention[33]. Furthermore, inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β have been reported to affect the differentiation of MSCs, possibly driving MSCs toward specific cell phenotypes, such as astrocytes. Elevated levels of such pro-inflammatory cytokines can inhibit neuronal differentiation and promote the differentiation of BMSCs into astrocytes[34]. In conclusion, under specific conditions, BMSCs can differentiate into SCs and neural-like cells both *in vitro* and *in vivo*, facilitating nerve repair through cell replacement.

Improving neural regeneration microenvironment

Neurotrophic factors have the function of promoting nerve growth and inducing cell differentiation into neural cells, and they can be used to induce the differentiation of BMSCs into neural cells. BMSCs can secrete a variety of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), NGF, vascular endothelial growth factor (VEGF), bFGF, and insulin-like growth factor (IGF)[14]. They upregulate the expression of VEGF receptor (VEGFR) and IGF1 receptor (IGF-1R) and promote the secretion of endogenous neurotrophic factors in the central nervous system. These neurotrophic factors are synthesized and retrogradely transported to nerve cells, transmitting information or paracrine signals to proximal and distal nerves. They bind to their specific receptors, such as NGF with NGF receptor A, BDNF with tyrosine receptor kinase B, and neurotrophin-3 (NT-3) and neurotrophin-4/5 with neurotrophic tyrosine receptor kinase 3. Activation or inhibition of signaling pathways such as PI3K/Akt, Ras-ERK, cAMP/PKA, and PLC-γ-dependent pathways occurs, thereby promoting neuron survival, accelerating axonal and vascular growth, stimulating nerve fiber regeneration, preventing cell apoptosis, inducing SCs migration, proliferation, and myelination formation, and slowing down muscle atrophy, thus reversing the negative effects of PNI (such as preventing cell death caused by axonal injury) [5,35-37]. This improves the supportive microenvironment for neuron survival and regeneration[38] and exerts a neuroprotective effect on nerve cells[39]. Neuhuber *et al*[40] suggested that the neurotrophic factors produced by human BMSCs are essential for mediating axonal growth and functional recovery after spinal cord injury.

Wang *et al*[41] conducted a study and reported that using BMSCs transplantation in rats with PNI achieved results similar to autologous nerve transplantation, possibly due to the release of a large number of neurotrophic factors by BMSCs. Isele *et al*[42] found that the growth condition medium of BMSCs significantly reduced cross-cell-induced apoptosis in fetal rat hippocampal neurons, demonstrating a significant neuroprotective effect. During this process, they observed an increase in phosphorylation of MAPK/ERK and Akt. Blocking this protective effect occurred when using MAPK/ERK and PI3K/Akt specific inhibitors, suggesting that the neurotrophic factors secreted by BMSCs counteracted apoptosis stress response by activating these survival pathways and exerting a neuroprotective effect. They also discovered that stressed neuronal cells stimulated BMSCs to increase the secretion of trophic factors. In another study by Yang *et al*[43], they used BMSCs as support cells and injected them into a silk fibroin-based nerve conduit. This approach increased the expression of the SCs marker molecule S100 and enhanced the secretion of various neurotrophic growth factors such as BDNF, bFGF, and ciliary neurotrophic factor (CNTF). This, in turn, facilitated histological and functional recovery in rats with sciatic nerve injuries.

The ECM is a complex reticular structure composed of large molecules such as proteins and polysaccharides secreted by cells. It includes laminin, fibronectin, collagen, and other components. The ECM plays a crucial role in promoting cell proliferation and differentiation, supporting the transmission of important signals in the peripheral nervous system[44], which, together with neurotrophic factors and cell adhesion molecules, provides a favorable microenvironment for the survival of nerve cells and the formation of nerve connections[45-47]. Chen *et al*[48] mixed BMSCs cultured *in vitro* with gelatin and transplanted them into a 15 mm defect model of the rat sciatic nerve using silicone conduits. Compared to the

gelatin-only control group, the experimental group showed improved walking behavior in rats, reduced atrophy of the gastrocnemius muscle, and decreased reduction in compound motor action potential amplitude, with a significant amount of regenerated axons observed. Both *in vitro* and *in vivo*, BMSCs synthesize and secrete various ECM components, including NGF, CNTF, BDNF, glial cell-derived neurotrophic factor (GDNF), as well as type I and type IV collagen, fibronectin, laminin, and other ECM molecules. After transplantation, both early and late stages of nerve regeneration are accompanied by high expression of neurotrophic factors. Wright *et al*[49] reported that BMSCs can stimulate neuronal development and mediate nerve regeneration by modulating the expression of ECM components such as chondroitin sulfate proteoglycans, myelin-associated glycoproteins, and Nogo-A.

Cell adhesion molecules are also critical for axon guidance, including integrins, neural cell adhesion molecules, and calcium-binding proteins such as N-cadherin. Among them, neural cell adhesion molecules may preferentially promote the growth of sensory axons[50]. BMSCs can express various factors related to cell adhesion, such as Ninjurins 1 and 2, Netrin 4, Robo 1, and Robo 4[51-53]. These factors are recognized as neuroregenerative factors and effectively promote axonal growth and cell migration. In summary, BMSCs improve the microenvironment for neuron survival and regeneration through paracrine secretion of neurotrophic factors, ECM factors, adhesion molecules, and various other mechanisms. By promoting the regeneration of damaged neurons, BMSCs contribute to the repair of neural functions.

Promoting angiogenesis

After PNI occurs, the blood vessels within the nerves are damaged. Therefore, promoting vascular regeneration and restoring blood circulation are essential for the recovery of the normal neural tissue environment. Peripheral nerve regeneration is closely related to angiogenesis, which is a crucial process in the repair of peripheral nerves. VEGF is considered an effective factor for both angiogenesis and neuron generation, and it has long been recognized for its importance in promoting neuron survival and SCs proliferation. Popovich *et al*[54] reported that BMSCs can secrete various neuroprotective trophic factors such as BDNF, NGF, and VEGF in an autocrine and/or paracrine manner, which can upregulate the expression of these factors, thereby promoting local microvascular regeneration, nerve regeneration, and reconstruction, and ultimately facilitating the repair of injured cells. Induced SCs-like cells from BMSCs have been found to exhibit enhanced immunostaining for VEGF, suggesting that BMSCs may also promote blood vessel formation [55]. BMSCs can also increase the expression levels of endogenous VEGF and its receptor VEGFR2 in the ischemic penumbra, thereby promoting neovascularization[15]. Zurita and Vaquero[56] also observed that blood vessel wall cells in newly regenerated neural tissue at the site of spinal cord injury were differentiated from injected BMSCs. These studies indicate that BMSCs can promote angiogenesis through paracrine secretion of VEGF, and the newly formed blood vessels can, in turn, facilitate the repair of peripheral nerve injuries.

Promoting myelination and axon regeneration

Myelination is another essential process in the regeneration of PNI, determining the quality and functional recovery of nerve regeneration[5,35,47]. Typically, myelination can be achieved by promoting endogenous repair mechanisms or providing an exogenous source of myelinating cells, leading to subsequent nerve function restoration[47]. In a study conducted by Kizilay *et al*[57], the systemic application of BMSCs was explored in a PNI compression model. Wistar albino rats were used, and the sciatic nerve was compressed for 5 min to create the model. Approximately 5×10^5 BMSCs were injected intravenously. The results showed that animals treated with BMSCs exhibited higher nerve conduction velocity, compound action potential, and axon numbers compared to the control group. In addition, myelin damage was less severe in the BMSC-treated group, suggesting that systemic application of BMSCs has a positive impact on both myelination and axon survival in the peripheral nerve compression model.

SCs and various types of adult stem cells (in the form of SCs-like cells) have the ability to form myelinating neuronal cells and regenerate nerves. During the regeneration process after PNI, intracellular cAMP levels are elevated when SCs or SCs-like cells further differentiate into myelin-forming cells. This leads to the synthesis and secretion of abundant myelin proteins, such as myelin basic protein, myelin protein zero, peripheral myelin protein 22 (PMP22), and other proteins that are crucial for myelin structure and function. This promotes remyelination during and after regeneration[5, 47] and increased expression of IGF-1R and neurofilament type 1 and type 3 enhances axon alignment and myelination gene expression, resulting in increased myelin thickness and internodal length[35,50]. BMSCs also provide various cytokines and growth factors for nerve regeneration[58], including NGF, NT-3, VEGF, PMP22[59-62], and more. Zhao *et al* [63] also demonstrated that exosomes from BMSCs upregulate the expression of PMP22, VEGF, NGF receptors, and S100β protein, promoting increased neuronal length and axon diameter in the dorsal root ganglion. These protein factors play crucial roles in peripheral nerve regeneration. During the repair process, BMSCs not only directly affect SCs through their neurotrophic functions[64] but may also differentiate towards SCs directionally.

BMSCs, in addition to their ability to differentiate into neuron-like cells[65], also stimulate and induce axonal growth [66], and play an important role in maintaining the normal structure and function of myelin sheaths[67,68]. BMSCs can promote the repair of damaged nerves by regulating the expression of myelination-related genes. For instance, differentiation of BMSCs into SC-like cells can enhance the mRNA expression of myelin-associated factors, significantly increasing the number of myelinated axons, thereby promoting the functional recovery of the facial nerve[69]. In conclusion, MSCs promote myelination and axonal regeneration through various mechanisms, including the secretion of neurotrophic factors, direct interactions with neurons, and upregulation of genes involved in myelination. These combined effects contribute to enhanced axonal growth and improved functional recovery after PNI.

Immunomodulation

After PNI, various immune cells and cytokines are present, and the coordination of local inflammatory response is

essential for the recovery of PNI. BMSCs possess significant immunomodulatory properties, which can promote neural tissue regeneration and alleviate inflammation, therefore making them valuable in PNI treatment. BMSCs can exert immunomodulatory effects by regulating the expression of various cytokines. IL-6 is a multifunctional cytokine produced by macrophages and fibroblasts during PNI[70]. IL-17 is produced by activated CD4+ T cells and can increase the production of pro-inflammatory cytokines and neutrophil chemoattractants, showing elevated levels after PNI[71]. Studies by Ge *et al*[72] found that BMSCs can secrete high levels of IL-6 to modulate the balance of CD4+ T cell subgroups, promote the proliferation and differentiation of T helper type 17 (Th17) cells that secrete IL-17, and subsequently stimulate prostaglandin E2 secretion. Elevated prostaglandin E2 levels then inhibit Th17 cell secretion of IL-17, achieving therapeutic effects for facial nerve injury. The increased expression of IL-10 protein is associated with regeneration of myelin protein. Research by Cui *et al*[73] revealed that IL-10-stimulated BMSCs can inhibit the expression of the pro-inflammatory cytokines TNF-α and IL-1β. Fan *et al*[74] suggested that this may be achieved by reducing the release of the pro-inflammatory cytokines IL-2, interferon-γ, and TNF-α and increasing the secretion of IL-10 in lymphocyte supernatant and serum, thereby promoting neural regeneration.

BMSCs can modulate the polarization of macrophages, promoting their transition from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This shift in macrophage polarization is crucial for controlling inflammation and establishing an environment for tissue repair and regeneration. Zhong *et al*[75] reported that BMSCs secrete GDNF, which converts the damaging M1 phenotype in microglia to the regenerative M2 phenotype, thereby suppressing neural inflammation. This process may be related to inhibiting the nuclear factor-kappaB signaling pathway and promoting the PI3K/AKT signaling pathway.

Another important aspect of MSC-mediated immune regulation is the release of extracellular vesicles (EVs), including apoptotic bodies, exosomes, microvesicles, *etc.*[76], which contain bioactive components. These EVs are considered an intriguing non-cellular therapy due to their low immunogenicity and ability to mediate cell-to-cell communication and modulate the function of recipient immune cells, contributing to the overall immunomodulatory effects of BMSCs. BMSCs' EVs may exhibit similar anti-inflammatory functions as BMSCs themselves by decreasing the levels of inflammatory cytokines and enhancing anti-inflammatory responses. For instance, Schäfer *et al*[77] found that BMSCs can release soluble mediators such as TNF-α and IL-1β to alleviate inflammation after PNI. It is evident that BMSCs can exert their immunomodulatory effects through various mechanisms, including regulating the expression of various cytokines, regulating macrophage polarization, releasing EVs, and secreting soluble factors. These effects can help control inflammation, prevent autoimmune reactions, and create a more favorable environment for nerve repair and regeneration following PNI.

In summary, BMSCs play a crucial role in promoting PNI repair and regeneration through various mechanisms (Table 1). First, BMSCs are able to differentiate into nerve cells (such as neurons and SCs) to replace damaged nerve cells and facilitate nerve regeneration. Second, they secrete neurotrophic factors, ECM molecules, and adhesion molecules, while also exerting immunomodulatory effects, creating a supportive microenvironment for the growth, differentiation, and survival of nerve cells. Third, BMSCs promote the formation of new blood vessels to ensure the necessary blood supply for the repair and accelerated regeneration of damaged nerves. Lastly, by synthesizing and releasing of proteins related to myelination and axon regeneration, BMSCs enhance the growth of myelinated axons and ultimately promote neuron regeneration. BMSCs utilize these different mechanisms to promote the repair and regeneration of damaged nerve cells and enhance the functional recovery after PNI. Utilizing these pathways can significantly enhance the therapeutic potential of BMSCs in PNI treatment.

APPLICATION METHODS OF BMSCS IN TREATMENT OF PNI

The unique mechanisms of action of BMSC make them promising candidates for the treatment of PNI. In this section, we will explore the various application methods of MSCs in PNI treatment (Figure 2), analyzing the advantages and disadvantages of each approach in order to comprehensively explore their potential in PNI treatment.

Direct transplantation

BMSCs have self-renewal and multi-lineage differentiation capabilities that make neuronal regeneration and nerve function recovery possible, rendering them one of the best choices for stem cell therapy in PNI treatment. Apart from their regenerative potential, BMSCs have been shown to migrate to the injury site and home to the injured area, exhibiting potential for targeted therapy[78,79]. Furthermore, BMSCs do not significantly stimulate the proliferation of T cells nor serve as a target for CD8+ T cells. Thus, when applied in autologous or allogeneic transplantation, they can evade the killing and clearance by immune cells in the body, further exerting their reparative effects. Cuevas *et al*[31] and Cuevas *et al*[80] cultured BMSCs from adult rats, labeled them with BrdU, and then injected them into the distal stump of the 5 mm-deficient sciatic nerve in rats. At 18 d and 33 d post-surgery, footprint analysis showed significant improvement in the motor function of the rat limbs compared to the control group injected with only culture medium. Immunofluorescence double-labeling showed that BrdU-labeled cells survived for at least 33 d after surgery, and nearly 5% of the cells expressed the S100 phenotype of SCs. In March 2004, they conducted a similar study on the long-term recovery of rat limbs 180 d after BMSC transplantation, finding that BMSCs continued to have a promoting effect on long-term recovery after surgery[80]. This experiment proves the great potential of BMSCs in peripheral nerve regeneration and lays the foundation for their application in the field of peripheral nerve regeneration. Wang *et al*[41] investigated the reparative effects of BMSCs by injecting them into the muscles after sciatic nerve injury in rats, and the results showed that the number of regenerating nerve fibers and spinal cord ventral horn neurons increased significantly, as well as a significant

Table 1 Mechanisms of bone marrow mesenchymal stem cell therapy for peripheral nerve injury

Mechanism	Key processes/factors	Description	Ref.
Differentiation into nerve cells	SCs, neurons	BMSCs differentiate into various nerve cells, including neurons, astrocytes, and Schwann cell-like cells, both *in vitro* and *in vivo*	[27-34]
Improvement of nerve regeneration microenvironment	Neurotrophic factors, ECM molecules, adhesion molecules, paracrine effects	BMSCs secrete neurotrophic factors, regulate ECM components, secrete adhesion molecules, and exert paracrine effects, creating a suitable microenvironment for nerve regeneration and functional recovery	[5,14,35-39,41-43,48,49,51-53]
Promotion of neovascularization	VEGF, endothelial cells	BMSCs secrete VEGF and differentiate into endothelial cells, participating in the process of vascular development and promoting the formation of new blood vessels	[15,54-56]
Enhancement of myelination and axon regeneration	Myelinating cells, myelin proteins, neurotrophic factors, Schwann cells	BMSCs promote myelination and axon regeneration by differentiating into myelinating cells or Schwann cells, secreting neurotrophic factors and regulating the expression of myelination-related genes, thereby improving nerve function	[5,47,57,63,64,66-69]
Immune modulation	Cytokine regulation, macrophage polarization, extracellular vesicles, soluble factors	BMSCs control inflammation, prevent autoimmune reactions, and create a favorable environment for nerve repair and regeneration by regulating the expression of various cytokines, modulating macrophage polarization, releasing EVs, and secreting soluble factors	[70-77]

SCs: Schwann cells; BMSC: Bone marrow mesenchymal stem cell; ECM: Extracellular matrix; VEGF: Vascular endothelial growth factor; EVs: Extracellular vesicles.

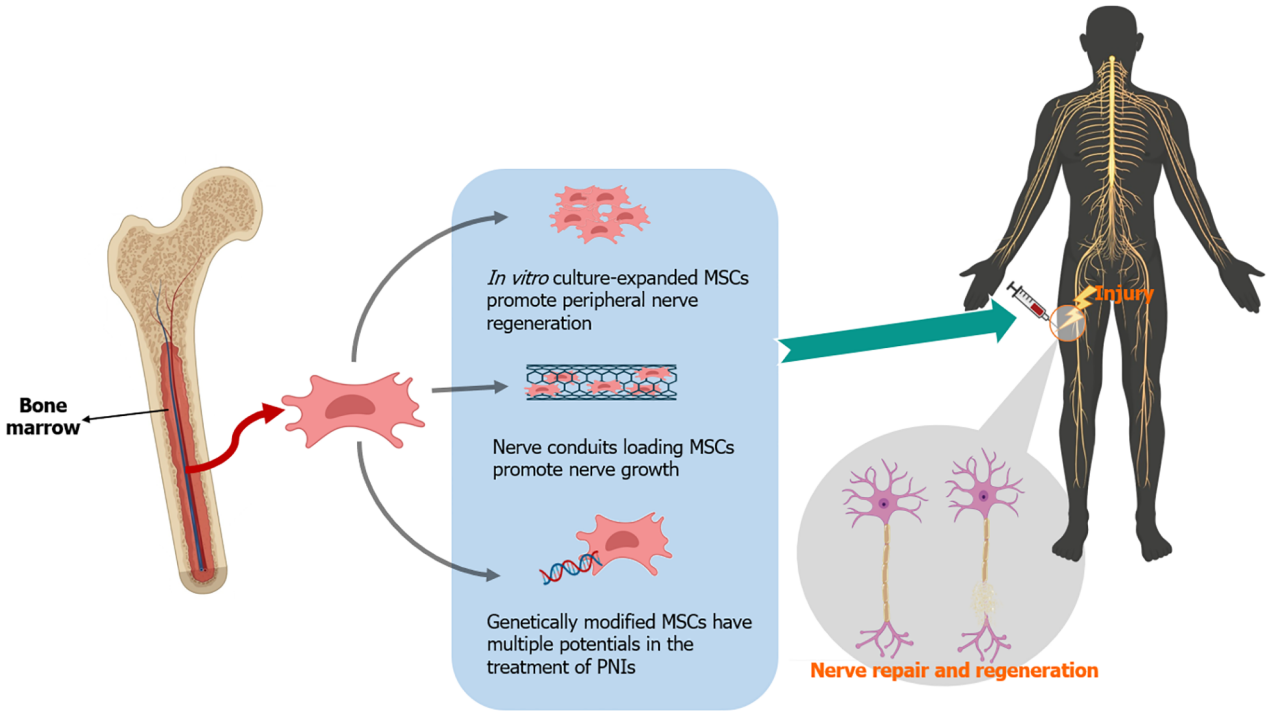

Figure 2 Application of bone marrow-derived mesenchymal stem cells in the treatment of peripheral nerve injury. Bone marrow-derived mesenchymal stem cells can be isolated from bone marrow, expanded *in vitro*, and directly transplanted into damaged nerve tissue. They can be loaded onto nerve conduits, which provide structural support, using tissue engineering techniques. Additionally, bone marrow-derived mesenchymal stem cells can be genetically modified with neurotrophic factors before being applied to the treatment of peripheral nerve injury to promote neuronal repair and regeneration. PNI: Peripheral nerve injury; MSC: Mesenchymal stem cell.

increase in regenerated myelin sheath thickness, which indicated that transplantation of BMSCs in PNI rats can achieve similar results as autologous nerve transplantation. Hu *et al*[81] transplanted BMSCs to repair a 50 mm midline nerve injury in monkeys and found that the healing process was similar to that of autologous transplantation, showing good functional and morphological outcomes. Another study found that when BMSCs were directly transplanted around the sciatic nerve stump, they induced axonal growth by differentiating into neuron-like cells and secreting neurotrophic factors[32]. They also differentiated into SCs to repair the injured nerves[33] and promoted remyelination of regenerating nerve fibers. From this, it can be seen that direct transplantation of BMSCs has played a positive role in repairing various PNI-damaged nerves. However, the invasive procedures required for obtaining BMSCs and the limited quantity of cells

obtained, as well as the reduced proliferative and differentiation abilities with increasing patient age, have restricted the research and application of BMSCs in clinical settings.

Tissue engineering

Scaffold technology has become a hot topic in tissue engineering research in recent years, and nerve conduits are a type of artificial tubular scaffold. BMSCs can simulate the structure and function of the human nervous system when loaded onto nerve conduits and connecting on both sides of the nerve stump. Nerve conduits can be made from natural materials such as chitosan and collagen or synthetic materials such as polyglycolic acid and polylactic acid. Each material has its own characteristics, generally inducing nerve axon regeneration and preventing infiltration of surrounding tissues to interfere with nerve repair. By loading BMSCs onto nerve conduits, not only does it achieve the neurotrophic guidance function of the nerve conduit, but it also provides a space for BMSCs and nerve axon regeneration induction, which helps to promote the effects of BMSCs in promoting nerve growth and regulating the microenvironment of the injury site[82]. In the process of repairing injured nerves using tissue engineering methods, comparing the transplantation effects of nerve conduits with and without BMSCs, it was found that the number and diameter of nerve axons in the experimental group significantly increased, and the improvement of nerve function was significantly better than that in the control group[83].

Costa *et al*[84] inplanted BMSCs into poly(L-lactic acid) nerve conduit scaffolds for repairing facial nerve defects in rats. The results showed that BMSCs could successfully integrate into the conduit, survive within the nerve tissue, and maintain their phenotype for up to 6 wk. In another study, researchers loaded BMSCs into chitosan nerve conduits and observed cell survival and proliferation within the conduit for 8-16 wk, which effectively promoted the repair of an 8 mm nerve defect[85]. Subsequent research by this team demonstrated that BMSC-loaded chitosan nerve conduits not only accelerated the efficiency of nerve repair but also improved the quantity and quality of regenerated nerve fibers, achieving therapeutic effects comparable to autologous nerve transplantation[86]. The degradation products of nerve conduit materials often trigger local immune reactions, leading to an inflammatory state at the site of injury, which can affect the repair outcome. However, in a study by Hsu *et al*[87], researchers modified chitosan nerve conduits with laminin to enhance the adhesion capability of BMSCs within the conduit. They observed that BMSCs successfully inhibited the local inflammatory response caused by chitosan degradation, resulting in improved promotion of nerve repair. Other experimental studies have also used BMSCs implanted in nerve conduits made of different materials, such as fibroin gel conduits[88], polylactic-co-glycolic acid conduits with ECM gel[89], and polyglycolic acid conduits[90], to intervene in PNI animal models, and all achieved favorable results.

Although encouraging results have been obtained in animal experiments, further research is still needed to optimize the design of nerve conduits, determine the optimal combination of BMSCs and biomaterials[91], and assess the long-term safety and efficacy of nerve conduits in clinical settings[92]. By addressing these issues, the use of BMSCs in tissue engineering approaches may have a more significant impact on PNI treatment, providing new strategies to promote neural functional recovery and improve the quality of life for patients.

Gene engineering

Gene-modified BMSCs have also gained increasing attention in tissue engineering research. In the field of neural repair tissue engineering, the main purpose of gene modification is to design target cells to overexpress growth factors, migration molecules, and adhesion molecules, as well as to inhibit the expression of defective genes. NT-3, NT-4, BDNF, NGF, CNTF, bFGF, and others are major neural growth factors suitable for peripheral nerve gene delivery, as they can provide a suitable microenvironment for the survival and axonal growth of BMSCs. In a study by Zhang *et al*[93] in 2015, BMSCs transfected with BDNF and CNTF were used for the treatment of rat sciatic nerve injuries. The results showed that BDNF- and CNTF-transfected BMSCs combined with nerve transplantation significantly improved the sciatic nerve function index, promoted the recovery of muscle activity, and increased the thickness of regenerating nerve myelin sheaths. This indicates that this approach is effective in promoting axonal growth and facilitates nerve repair in PNI. In another study[94], BDNF was successfully transfected into BMSCs using gene engineering technology, and the transfected BMSCs were combined with decellularized allogeneic nerve grafts to repair peripheral nerve defects. The results showed a significant improvement in the repair effectiveness of the nerve grafts and the morphology of the injured nerves. Gene-modified MSCs have multiple potentials in the treatment of PNI. However, since gene therapy is still in the experimental stage, its application in clinical settings requires addressing numerous challenges, such as the selection of diverse target genes, stable expression of target genes in the host, combination therapy with multiple genes, and ethical considerations.

CONCLUSION

Unlike the central nervous system, the peripheral nervous system has the ability for self-regeneration and repair after injury. However, this endogenous repair is limited, and extensive nerve damage cannot be fully repaired. Cell therapy is considered to be an important direction for future medical development, and in recent years, the field of PNI neural regeneration and repair has made vigorous progress, with enormous market potential and clinical application value. BMSCs have the advantages of abundant sources, easy and simple procurement, being easy to isolate and cultivate, and the potential for rapid expansion under certain conditions. Additionally, autologous BMSCs transplantation avoids ethical issues and immune rejection, offering broad prospects for PNI treatment. In this paper, we have reviewed the current biological characteristics of BMSCs related to PNI, summarized the mechanisms by which BMSCs promote PNI

neural regeneration and repair, and explored various application methods of BMSCs in PNI, confirming the potential of BMSCs in treating PNI.

However, most research on BMSCs transplantation for PNI intervention is still in the pre-clinical stage and has not yet had significant implications for clinical practice, and there are also certain limitations, such as the lack of specific surface markers on BMSCs[21], which poses some difficulties in identifying cultured BMSCs, and the lack of standardized treatment regimens, where many times after BMSC transplantation, the survival rate is not high, and the proportion of differentiation into neurons is low, resulting in unsatisfactory nerve repair effects. There are also safety issues with BMSC transplantation, where inducers transplanted into the human body along with BMSCs can cause varying degrees of damage to the human body, and there is a possibility of BMSCs transforming into malignant tumors[95]. These issues that need to be resolved point to a certain direction for future research, such as establishing standardized procedures for the extraction, identification, and cultivation of BMSCs; further clarifying the therapeutic mechanisms of BMSCs; and observing the safety of BMSCs applications. The choice of BMSCs application methods in PNI, such as direct transplantation, tissue engineering, and gene engineering, also requires further investigation. In conclusion, BMSCs transplantation offers broad prospects for PNI treatment, but significant theoretical and experimental research are needed before its clinical application can be fully developed and perfected.

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