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Review

Beyond conventional therapies: MSCs in the battle against nerve injury

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ABSTRACT

Nerve damage can cause abnormal motor and sensory consequences, including lifelong paralysis if not surgically restored. The yearly cost of healthcare in the United States is projected to be $150 billion, and millions of Americans suffer from peripheral nerve injuries as a result of severe traumas and disorders. For nerve injuries, the outcome of conventional therapies is suboptimal and may have unfavorable side effects. However, mesenchymal stem cells (MSCs) have been proven to be a viable option for the reconstruction of injured nerve tissue and bring a ray of hope. These stem cells are derived from bone marrow, adipose tissue, and human umbilical cord blood and have the ability to secrete trophic factors, contribute to the immune system, and stimulate axonal regeneration. The purpose of this review is to examine the potential benefits of MSCs for enhancing functional recovery and patient prognosis by highlighting their characteristics and elucidating their mechanism of action in nerve injury healing.

Contents

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1. Introduction

Nerve injuries can result in severe motor and sensory sequelae, frequently with functional deficits [1]. These sequelae can occur in many stages, from simple conduction blocks to complete nerve transections, as described in studies by Goubier et al. [1] and Sunderland et al. [2]. Without surgical repairs, these injuries can cause permanent paralysis, putting a great deal of financial burden on patients as well as society. Peripheral nerve injuries arising from trauma and medical conditions affect about 20 million Americans, and the yearly cost of healthcare in the US is estimated to be $150 billion [3,4]. Both nerve injuries and their aftereffects endanger patients' quality of life, so new approaches to address these difficulties are necessary. Because of the nerves' limited capacity for self-healing and the inability of conventional treatments to fully restore their functions, treating nerve injuries has always been difficult and has frequently resulted in crippling side effects like loss of sensation, impaired motor function, and chronic pain. Optimal healing is still elusive despite advancements in surgical procedures and rehabilitation therapies.

In recent years, mesenchymal stem cells (MSCs) have emerged as a viable option for the regeneration and repair of damaged nerve tissue [5,6]. These MSCs can be obtained from easily accessible sources such as bone marrow, adipose tissue, and human umbilical cord blood. And they all can differentiate into Schwann cell-like cells (SCLCs), a kind of regenerative cell that can restore function even in the event of nerve damage [7] due to their properties of secreting trophic factors, regulating the immune system, and promoting axonal regeneration [8]. Multiple experimental studies have demonstrated that a variety of methods can help promote nerve repair and functional recovery. Low-energy laser irradiation elevates neuronal activity and increases the expression of neurotrophic factors that support the growth of nerve protrusions [9]; magnetic stimulation accelerates peripheral nerve regeneration, and low-frequency magnetic stimulation in particular contributes to selective muscle reattachment [10]; vitamin D2 stimulates axon regeneration [11]; and supplementation with acetyl-L-carnitine [12,13] and fermented soy beans [14] supports nerve healing and functional recovery by increasing the aerobic capacity of neurons and ameliorating neurobehavioral deficits to promote nerve repair.

In this review, we focus on the properties of the MSCs that are capable of differentiating into Schwann cell-like phenotypes, releasing neurotrophic factors that contribute to anti-inflammation in the repair of neurological injuries. By revealing the properties of diverse origins of MSCs and the mechanisms that drives repair, the present review seeks to elucidate the potential of MSC-based therapies in promoting functional recovery and leading to an enhanced prognosis for patients with neurological injuries, thereby highlighting the promise of MSC-based regenerative therapies in patients with neurological injuries.

2. Characterization differences between AD-MSCs, BM-MSCs and UC-MSCs

Although the adipose-derived Mesenchymal Stem Cells (AD-MSCs), the bone marrow-derived mesenchymal stem Cells (BM-MSCs) and the umbilical cord-derived mesenchymal stem cells (UC-MSCs) all possess self-renewal and differentiation potential, their biological properties differ significantly. AD-MSCs exhibit a strong adipose differentiation ability and low immunogenicity, thus they are primarily used for fat reconstruction and immunomodulatory therapy in clinical applications; while BM-MSCs originate from the bone marrow, have a relatively high hematopoietic supportive function, and are capable of differentiate into a variety of cell types, such as bone, cartilage and muscle; whereas UC-MSCs, because they are derived from umbilical cord tissue at the embryonic stage, exhibit strong immune tolerance and higher differentiation potentials, especially in neurological-related therapies. Distinct origins of MSCs exhibit different embryonic lineages during development, which may be an essential reason for the discrepancy of their characteristics. AD-MSCs originate from adipose tissue, and their developmental process is closely related to mesoderm, whereas BM-MSCs derive from the hematopoietic microenvironment, which is influenced by development of hematopoietic stem cells. UC-MSCs, which originate from the umbilical cord, with cells that originate from the early embryonic stage of development, may retain some of the properties of early stem cells, which enables them to show unique advantages in specific therapies.

The neural crest is a temporary embryonic tissue that appears during neural tube formation and contains cells with strong migratory and differentiation potential, with the ability to differentiate into specific cell types in accordance with their locations [15]. According to Morikawa et al. (2009), neural crest cells (NCCs) are one of the cells from which MSCs originate [16], and they share several characteristics with MSCs, especially during development when they both have specific migratory and pluripotent capacities. While NCCs can differentiate into various cell types, such as

neurons, glial cells, etc., which is similar to the fact that MSCs are capable of differentiating into a range of cells, such as adipose, bone, cartilage, etc. The development of UC-MSCs is linked to neural crest cells to a certain extent, especially in the treatment of neurological disorders, and UC-MSCs may act through a similar mechanism to that of NCCs. Besides, both AD-MSCs and BM-MSCs showed similar pluripotency to neural crest cells in some cases, especially in their potential for nerve regeneration. Thus, neural crest cells may play a guiding role in the differentiation potential and therapeutic role of MSCs, especially in the treatment of specific diseases. In-depth studies on the developmental mechanisms of different MSCs sources could lead to a better understanding of their heterogeneity and provide a theoretical basis for their personalized treatment in clinical applications. The relationship between MSCs and neural crest cells should be further explored in future investigations to disclose the underlying mechanisms and generate more theoretical evidence for the utilization of the MSCs in regenerative medicine.

3. Schwann cells and repair Schwann cells

Several studies conducted by Jessen et al. [7,17–19] have summarized the main differences in the function and phenotypic characteristics between Schwann cells (SCs) and repair Schwann cells (RSCs). SCs in intact nerves are typically responsible for myelination and axonal support by wrapping multiple smaller axons to enhance signal conduction and protect against external stimuli [20]. However, upon nerve injury, myelinated SCs become activated and convert to the RSCs, a specialized subtype that are primarily responsible for facilitating the repair process rather than maintaining nerve function.

In response to injury signals, the myelinated SCs undergo a process of activation, de-differentiation, and acquisition of repair-specific features governed by the upregulation of specific transcriptional factors, e.g. c-Jun, including upregulation of trophic factors [21], activation of autophagy to breakdown myelin sheaths [22,23], and formation of guiding trajectories (Bungner's bands) [21], which promote axon regeneration and guide regenerated axons back to target tissues [24].

Suzuki et al.'s experiments [25] revealed the differences between SCs and RSCs in terms of morphology, regenerative function, and molecular profile. Morphologically, RSCs are more elongated with numerous cellular processes that better adhere and promote neuronal growth [26]. Molecularly, RSCs upregulate genes that are associated with inflammation, repair, and regeneration driven by elevated c-Jun expression [27], whereas SCs focus on myelin maintenance [28], Notch signaling [29], and aging. Thus, SCs in intact nerves support the maintenance of axon integrity through myelination or demyelination (Remak), whereas RSCs are adaptive to repair and regenerate the nerve after injury. Such adaptive responses ensure the survival of injured neurons and promote axonal regeneration, thus highlighting the important role of Schwann cell plasticity in peripheral nerve repair.

Nevertheless, due to the time-consuming and secondary complications at the donor site when obtaining these SCs from nerves, it is necessary to investigate alternative cell sources, particularly, MSCs of different tissue origins, that possess the same potential to generate SCs.

4. Adipose-derived mesenchymal stem cells

4.1. Differentiate into a Schwann cell-like phenotype

The AD-MSCs exhibit remarkable properties, such as the ability to differentiate into SCLCs phenotypes [30–33], which perform an important role in the repair of nerves. Such ability of AD-MSCs makes them an attractive candidate in the field of regenerative medicine, especially in the treatment of nerve injury and related disorders. The transformation of AD-MSCs into SCLCs provides a pathway to promote nerve regeneration and has the potential to revolutionize therapies for the treatment of peripheral neurological disorders.

SCs are the main support structures of the peripheral nervous system. They play a crucial role in the promotion of recovery and regeneration after a nerve injury. A major function is their capacity to secrete neurotrophic factors, which are essential for establishing a supportive microenvironment that promotes axonal regeneration [30] and myelin reformation [34]. Such capacity serves a vital role in regenerating nerve function and maintaining the structural integrity of nerve fibers after injury.

They can also stabilize the myelin sheath within the nervous system and transform into a phenotype that promotes myelin production during nerve repair [35–37]. Their dual function highlights the importance of their therapeutic approach in the improvement of neurological function and recovery, offering a promising path to address issues related to myelin degradation or injury. This remarkable ability highlights their effectiveness in the advancement of medical therapies that address neurological disorders and injuries, representing a significant advancement in the fields of neurobiology and regenerative medicine. Thus, it may be utilized as an initial intervention strategy to promote the healing of peripheral nerve injuries [38].

4.2. Neurotrophic factors (NTF) and reduce the inflammatory response

Secondly, AD-MSCs release neurotrophic factors, including nerve growth factor (NGF) [39–41], vascular endothelial growth factor (VEGF) [42], and brain-derived neurotrophic factor (BDNF) [43], which enhance angiogenesis and support cellular repair processes. Additionally, their secretome modulates the inflammatory response, reducing pro-inflammatory cytokines and increasing anti-inflammatory factors such as interleukin-10 (IL-10), which creates a favorable environment for nerve healing [31]. Furthermore, AD-MSCs' capacity to form three-dimensional spheroid structures serves to augment their secretory activity and therapeutic potential in contexts of nerve injury [44].

The study conducted by Dar et al. [45] demonstrated that AD-MSCs have the capacity to stimulate axon outgrowth and regeneration through the secretion of neurotrophic factors, including glial cell lineage-derived neurotrophic factor (GDNF), which has been shown to prevent neuronal death [46]. Additionally, AD-MSCs enhanced the expression of adhesion molecules (N-Cad), thereby facilitating the growth and adhesion of regenerated axons [47]. Furthermore, at the histological level, AD-MSCs can mitigate myelinolysis and Wallerian degeneration while promoting myelin sheath formation, thereby facilitating structural nerve repair.

In addition, neurotrophic factors also exhibit anti-inflammatory properties [30,48] that can reduce the adverse effects of long-term inflammation. By releasing these factors, AD-MSCs can provide a more favorable environment for tissue repair, reduce the level of proinflammatory cytokines, and promote the reduction of inflammation [49], thus improving the functional recovery [50,51]. Such dual action not only protects the surrounding nerve tissues from injury but also accelerates the process of repair.

4.3. Differentiated and undifferentiated AD-MSCs

A study conducted by Kingham et al. [33] illustrated that AD-MSCs differentiated into a SCs phenotype can induced more

axonal outgrowth and angiogenesis within the nerve conduit than undifferentiated adipose-derived mesenchymal stem cells (uAD-MSCs). It was shown that differentiated AD-MSCs (dAD-MSCs) exhibited significantly higher levels of the expression of neurotrophic and angiogenic factors, including VEGF-A and angiopoietin-1. These factors enhanced vascularization and axonal regeneration that were observed in the conduits that contain dAD-MSCs. A quantitative analysis also displayed that conduit containing dAD-MSCs had more extensive capillary-like tube formation and higher RECA-1 staining, suggesting enhanced vascularization. In addition, a significant increase in axonal growth distance was observed among animals in the dAD-MSCs-treated group compared with the uAD-MSCs-treated group or the cell-free control group. Thus, neurotrophic and angiogenic factors produced by dAD-MSCs may enhance the recovery of injured nerves through vascularizing areas and promote nerve regeneration [52].

According to a study performed by Tomita et al. [53] in 2013, the transplantation of differentiated human adipose-derived stem cells (dhASCs) in vivo significantly improved myelin formation and nerve survival as compared to undifferentiated human adipose-derived stem cells (uhASCs) in a rat tibial nerve compression model. More specifically, dhASCs resulted in a 10-fold improvement in myelin formation and a 7-fold improvement in nerve survival in contrast to uhASCs. Such improvements indicate that the in vitro differentiation process is an effective stimulus for inducing glial differentiation and improving the regenerative capacity of transplanted cells. While Kappos et al. ‘s findings [54] also illustrated that the dAD-MSCs were significantly superior to the uAD-MSCs in terms of improvement in muscle atrophy and functional recovery. The rats treated with dAD-MSCs had less muscle atrophy and better functional outcomes as measured by the sciatic nerve function index (SFI). More specifically, the mean SFI was higher for the dAD-MSCs group than the uAD-MSCs group, and the relative muscle weight was higher on the surgical side of the rats treated with dAD-MSCs compared to the AD-MSCs group. This suggests that differentiation of AD-MSCs to Schwann cell-like phenotype benefits nerve repair.

However, an experiment conducted by Orbay et al. [55] found that the dAD-MSCs did not significantly improve the therapeutic effect compared with undifferentiated cells. Watanabe et al. [56] also compared uAD-MSCs, dAD-MSCs, and SCs in a rat model with nerve injury, concluding that nerve regeneration capacity was the same in each group, as well as that the cell-based treatments provided commensurate functional results with self-grafts. By comparing the AD-MSCs and SCs, Sowa et al.'s experiment [57] also demonstrated that AD-MSCs significantly promoted axonal regeneration, myelin sheath formation, and the recovery of muscle atrophy to a level equivalent to the transplantation of Schwann cells. These results suggest that AD-MSCs can effectively support peripheral nerve regeneration without differentiating into SCLCs.

Both dAD-MSCs and uAD-MSCs have a promoting effect on the repair of nerves after injury, and future studies should consider the additional time and cost required for the differentiation of AD-MSCs, as well as their effects on the ability to repair nerves. In summary, as a potential cellular therapeutic tool, AD-MSCs show promising applications and important research significance in nerve injury repair.

5. Bone marrow-derived mesenchymal stem cells

5.1. Differentiate into a Schwann cell-like phenotype

The BM-MSCs can be induced to differentiate into a Schwann cell-like phenotype by a specific culture condition and growth factors [58]. These differentiated cells exhibit morphologic and functional characteristics that are similar to those of natural SCs [58,59] and are capable of mimicking the natural functions of SCs [60]. The Schwann cell-like phenotype from BM-MSCs can provide myelin sheaths for regenerating axons [61], which is a key function for restoring nerve function [62]. By mimicking the regenerative environment provided by natural SCs, the BM-MSC-derived Schwann cell-like phenotype contributes significantly to the repair and functional recovery of injured peripheral nerves [63,64].

BM-MSC-derived SCs can provide a supportive environment for axonal regeneration and myelin re-formation, thereby promoting peripheral nerve regeneration. Ao et al.'s research [65] also supports this point of view. A favorable three-dimensional matrix may be formed when these cells are seeded into a chitosan conduit and combined with a Matrigel matrix, which promotes the alignment and directional growth of regenerating axons. Such an environment mimics the behavior of natural SCs, which support nerve repair by forming “Schwann tubes” that guide axons and promote them to access distal nerve stumps in a timely manner. BM-MSCs-derived Schwann cells maintain their phenotype and ability to myelinate, ensuring an effective nerve repair that is comparable to that of autologous transplantation without the ethical issues associated with embryonic stem cells.

5.2. Neurotrophic factors and reducing the inflammatory response

One of the major benefits of using differentiated BM-MSCs-derived Schwann cell-like phenotypes is that they can secrete neurotrophic factors, which are essential to nerve regeneration [66]. These factors include NGF [67–69], BDNF [70–74], and GDNF [75,76] to support the survival and growth of neurons. These cells can also produce anti-inflammatory cytokines that promote an anti-inflammatory phenotype in macrophages [77–79], which helps to minimize secondary injury processes. Furthermore, the BM-MSCs exhibit homing properties and can migrate to the site of injury to exert paracrine effects and create a favorable environment for tissue repair [80]. This includes modulating the inflammatory response, reducing glial scar formation, and facilitating angiogenesis through the secretion of VEGF [81,82], as well as other pro-angiogenic factors. Moreover, several animal models [77,83] have shown that BM-MSCs can improve motor function, reduce fibrosis, and support the survival and proliferation of neuronal cells without causing significant adverse effects [84].

The neurotrophic support provided by these cells not only promotes axonal regeneration [85], but also enhances synaptic plasticity and functional recovery [86]. BM-MSCs can secrete neurotrophic and anti-apoptotic factors in neurological injuries such as brachial plexus injury, thus promoting the regeneration of neuronal cells and protecting injured neurons, thereby facilitating recovery. Furthermore, BM-MSCs are shown to have the ability to migrate to the site of injury and assist in the repair of injured neurons by regulating the MAPK/ERK pathway, which is essential for nerve repair.

5.3. Differentiated and undifferentiated BM-MSCs

Ladak et al.'s research [87] found that the electromyographic (EMG) measurements were the same in the empty conduit, undifferentiated mesenchymal stem cells (uMSCs), and differentiated mesenchymal stem cells (dMSCs) groups and were significantly lower than in the autograft and contralateral normal control groups. Although the effects of dMSCs were similar to those of SCs in promoting axonal regeneration and supporting neurite growth in vitro, they did not translate into significant functional reinnervation in vivo. Analysis of muscle weight and EMG could not distinguish differences in regeneration success between the nerve

conduit groups, which indicates that despite the neurotrophic effects of dMSCs, they are less effective than autografts in muscle reinnervation. Mathot et al.'s study [88] also indicated that both types of cells have varying states and functions. Although both cell types have the potential for nerve regeneration, the uMSCs have a real advantage for clinical applications as they do not require additional time and cost for differentiation and are faster to prepare. While both cell types significantly improved the functional outcome of nerve repair, uMSCs were more effective in improving isometric muscle tone and compound muscle action potentials after 12 weeks compared to dMSCs. Therefore, uMSCs are considered to be more advantageous in the treatment of sciatic nerve injuries due to their high efficiency and less preparation requirements.

A study conducted by Choi et al. [61] using a rabbit model indicated that axons could be regenerated by transplanting BM-MSCs into nerve defect sites, especially after embedding them in collagen gels. The number and diameter of myelin fibers increased in BM-MSC-treated areas compared to the controls. Chopp et al.'s research [89] also demonstrated that transplantation of BM-MSCs into the injured rat spinal cord significantly restored their function. Keilhoff et al. [62] concluded that the differentiated BM-MSCs (dBM-MSCs) could be transformed into SCLCs that promote neoangiogenesis and support nerve regeneration, which are more effective than undifferentiated BM-MSCs (uBM-MSCs). They can provide a better nutrient and supportive environment for regenerating nerves and exhibit better myelination capacity, which leads to improved regeneration. In addition, dBM-MSCs can reduce connective tissue fibrosis in grafts and show a stronger ability to induce early revascularization. In contrast, uBM-MSCs lacked significant regenerative capacity and were not effective in supporting extensive nerve regeneration.

The use of autologous BM-MSCs minimizes the risk of immune rejection and the ethical issues related to other cell sources as well. Enhancing neural repair and functional recovery following peripheral nerve injury can be accomplished using a scalable and efficient strategy by using the Schwann cell-like phenotype produced from BM-MSCs. Following studies, efforts ought to concentrate on refining differentiation procedures and assessing the enduring effectiveness and security of these cells within clinical settings. Compared to AD-MSCs, BM-MSCs showed better healing outcomes in terms of clinical, histopathologic, and gene expression analyses, but further clinical studies are needed to demonstrate this [45].

6. Umbilical cord-derived mesenchymal stem cells

6.1. Differentiate into a Schwann cell-like phenotype

The UC-MSCs have shown a remarkable ability to differentiate into a Schwann cell-like phenotype under appropriate conditions. SCs perform a crucial role in peripheral nerve repair and regeneration by providing support for regenerating axons. There are specific markers such as S100, GFAP, and p75, MBP, that are expressed when the induced UC-MSCs possess the characteristics of SCs. These cells are not only morphologically similar to SCs, but they also exhibit functional properties that are critical for nerve regeneration. Studies conducted by Peng et al. also indicated that transplantation of these UC-MSC-differentiated Schwann-like cells to the site of nerve injury can significantly promote axonal regeneration and accelerate functional recovery, thus highlighting their therapeutic potential [90,91].

Matsuse et al.'s findings [92] demonstrated that Umbilical cord-derived Schwann cells (UC−SCs) support axonal regeneration and myelin reformation through several essential observations. Both immunohistochemistry and immunoelectron microscopy showed the myelination of regenerating axons by UC-SCs, similar to human SCs. The transplanted UC-SCs expressed myelin-related proteins (MAG, PMP22, and periaxin) and formed myelin sheaths around the axons. Functional recovery was evaluated by the sciatic nerve function index (SFI), which showed that the UC-SCs group exhibited significant improvement over the control as well as the UC-MSCs group. In addition, the UC-SCs group had a higher density of positive nerve fibers and myelin markers and neurofilament proteins, indicating significant nerve regeneration and myelination. Together, these results suggest that UC-SCs have similar properties to those of SCs and contribute to axonal regeneration as well as myelin reconstruction after peripheral nerve injury.

6.2. Neurotrophic factors and reducing the inflammatory response

Several studies [93,94] have shown that collagen/silk fiber scaffolds (CSFSs) could promote the recovery of motor function by supporting nerve fiber regeneration and reducing the formation of glial scars. Within mice, the human UC-MSCs promoted functional recovery by decreasing IL-7 expression [95], modulating inflammatory responses, and enhancing the survival of myelin and neuronal cells. Additionally, human UC-MSCs altered Th1 and Th2 cytokine production [95], which further supported repair and recovery. By using 3D-printed scaffolds infused with human UC-MSCs secretome, the researchers observed nerve fiber regeneration, myelin sheath re-formation, enhanced synaptic connectivity, improved motor evoked potentials, and significant recovery of motor function in spinal cord injury (SCI) rats. These findings suggest that human UC-MSCs contribute to a favorable microenvironment for nerve regeneration and functional recovery.

It was shown that UC-MSC-conditioned medium enhanced the viability and proliferation of SCs, thus significantly increasing the expression of NGF and BDNF in SCs [96]. Additionally, UC-MSC-conditioned medium also promoted the growth of neurons in dorsal root ganglion explants. Analysis of cytokine antibody arrays and enzyme-linked immunosorbent assays (ELISA) demonstrated that UC-MSCs expressed and secreted a variety of neurotrophic factors [97], including BDNF, GDNF, HGF, NT-3, and bFGF. Immunostaining confirmed the presence of extracellular matrix proteins such as type I collagen, laminin, and fibronectin, which are essential for peripheral nerve regeneration. Collectively, these findings suggest that UC-MSCs can promote nerve repair through a paracrine mechanism, secreting growth factors and extracellular matrix proteins to create a favorable environment for nerve regeneration.

6.3. Differentiated and undifferentiated UC-MSCs

Previous investigation performed by Peng et al. [90] indicated that differentiated Wharton's Jelly derived-mesenchymal stem cells (dWJ-MSCs) demonstrated significant differences compared to undifferentiated Wharton's Jelly derived-mesenchymal stem cells (uWJ-MSCs) by immunocytochemical staining, RT-PCR, and western blotting analysis. In terms of function, when co-cultured with dorsal root ganglion neurons, WJ-MSCs differentiated into a SCLCs exhibited enhanced neurite development and released higher quantities of neurotrophic factors (BDNF, NGF, NT-3), in contrast to uWJ-MSCs. In contrast, fewer neurotrophies are produced by uWJ-MSCs, and they do not express SC markers, which suggests that their support for nerve regeneration is restricted. These distinctions emphasize the possibility of dWJ-MSCs as an alternative to SCs for nerve healing.

7. Other MSCs

Other than those three frequently and widely utilized sources of MSCs, the gingival-derived mesenchymal stem cells (GMSCs)/human

dental pulp stem cells (hDPSCs) and porcine skin-derived mesenchymal stem cells (pSMSCs) sources have also been shown to have a beneficial effect on the repair of nerves following nerve injury. Zhang et al.'s results [98] revealed that the GMSCs could promote nerve regeneration by their *trans*differentiation ability to induced neural progenitor cell-like cells (iNPCs), as well as their regulatory effect on Schwann cells. GMSCs could be induced into iNPCs under specific culture conditions without the need to introduce exogenous genes. Remarkable effects of axonal regeneration and remyelination were observed after transplantation of GMSCs and iNPCs into injured rat sciatic nerves. Immunofluorescence and western blotting analyses showed that local application of these cells could dynamically upregulate the expression of both neuronal and Schwann cell markers. Mechanistically, GMSCs and iNPCs promote nerve regeneration possibly by regulating the expression of a transcription factor, c-Jun, that governs the formation of repair SCs, and the expression of a transcription factor, Krox-20/EGR2, that is essential for Schwann cell myelination. In the following year, Carnevale et al.'s results [99] also demonstrated that hDPSCs have the ability to differentiate into Schwann cell-like cells, which are crucial in the repair of peripheral nerve injury. Those SCLCs can promote neurite growth and axon regeneration and facilitate the functional recovery of injured nerves. And hDPSCs can express markers such as STRO-1, c-Kit, and CD34 and secrete neurotrophic factors such as BDNF, NGF, and NT-3, which support nerve regeneration.

A study by Park et al., in 2012 evaluated the potential of pSMSCs for peripheral nerve regeneration [100]. Those cells showed MSCs properties and differentiated into mesenchymal lineages that showed neurogenic properties in vitro. For in vivo application, the pSMSCs labeled with PKH26 dye were transplanted into a femoral nerve defect model in miniature pigs using fibrin glue scaffolds. After 2 and 4 weeks of transplantation, the transplanted pSMSCs promoted remarkable nerve regeneration as evidenced by the formation of histologically intact nerve bundles and increased expression of neurotrophic factors [101] (e.g., S100 and p75NGFR). This study demonstrates that the combination of autologous pSMSCs with fibrin glue scaffolds can effectively induce peripheral nerve regeneration.

8. Animal models and clinicals trials

A recent review conducted by Lischer et al., in 2023 showed that significant evidence based on various large animal models (e.g., rabbits, dogs, sheep, and rhesus monkeys) suggests that MSCs may be one of the most promising therapeutic sources for the treatment of neurological injuries [102]. Another rat's model with peripheral nerve conducted by Tomita et al. [53] also demonstrated that transplanted AD-MSCs were able to promote peripheral nerve regeneration. Several animal models with peripheral nerve injury have shown that transplantation of BM-MSCs can improve the functional outcome, which includes enhancement of nerve conduction and muscle nerve regeneration [62,103]. In this review, we have included additional animal studies on the use of MSCs for nerve injury from the year of 2019 to the present. These studies are summarized in Table 1 below.

More than 1500 clinical trials have been documented in the clinicaltrials.gov database alone for the treatment of various diseases with MSCs, yet there are very few clinical trials on the use of MSC-based regenerative therapy for nerve injury repair. As of today (Dec 23, 2024), there are 7 registered trials using MSCs to treat nerve injury and 32 trials to treat SCI in the public clinical trials database (ClinicalTrials.gov) (Table 2). Typically, pharmaceutical products must undergo at least three phases of clinical trials before they can be registered and marketed by the appropriate drug regulatory authorities, and some drugs may require phase 4 clinical trials after they have been marketed. Approval for commercialization is contingent upon the clinical trials demonstrating the product's safety and effectiveness. Clinical trials in phases 1–4 are often carried out in a sequential manner, allowing for the completion of each phase only after the completion of the previous one. Generally speaking, two non-simultaneous clinical studies cannot be carried out simultaneously.

However, up to now, the majority of clinical trials regarding nerve injury and repair have remained concentrated in clinical phases 1 and 2, which may be due to a variety of reasons, such as but not limited to the relatively few qualified participants enrolled and lost to follow up during the long-term follow-up period of the trials; insufficient funding during the research process, and the willingness of the participants and their relatives to change their minds, etc.

As for the treatment of nerve-related injuries with MSCs, although only a few trials have reached a stage of progress and posted their results on the ClinicalTrials.gov system, their results have proven the feasibility of MSC therapies and have contributed to the positive impact of further explorations in the future. As early

Table 1
Selected studies of MSCs for nerve injuries in animals (From 2019–2024).

Study	Species	Nerve Graft Composition	Cell Source	Injury type	Duration (days)
Schilling 2019 [104]	Rats	Collagenase II	AD-MSCs	15-mm defect sciatic nerve	42
Mesentier 2019 [105]	Rats	Not applicable	BM-MSCs	Optic nerve crush	240
Zhang 2020 [106]	Rats	HO–PSNCs *	BM-MSCs	10-mm sciatic nerve defects	90
Deng 2020 [94]	Rats	Collagen/silk fibroin scaffolds (CSFSs)	UC-MSCs	Spinal cord injury (SCI)	56
Mathot 2021 [88]	Rats	Allografts	MSCs	10-mm sciatic nerve defect	112
Rodríguez-Sánchez 2021 [107]	Rats	Polycaprolactone (PCL) nerve guidance conduits	AD-MSCs	12-mm gap sciatic nerve damage	84
Daradka 2021 [108]	Mongrel dogs	Autologous saphenous vein graft	BM-MSCs	10-mm facial nerve defect	56
Wu 2021 [109]	Rats	Matrigel matrix	AD-MSCs	5-mm segmental nerve defect in the right sciatic nerve	7
Zhang 2021 [110]	Rats	Collagen hydrogel	GMSCs	6-mm gap facial nerve	98
Schaakxs 2021 [111]	Rats	PHB strips*	AD-MSCs	10-mm gap sciatic nerves	42
Chen 2022 [93]	Rats	Collagen/silk fibroin scaffolds (CSFSs)	UC-MSCs	2-mm spinal cord segment	56
Dar 2023 [45]	Rabbits	Collagen I	AD-MSCs BM-MSCs	Left limb incised 7-cm to expose the sciatic nerve	90
Zhang 2023 [112]	Rats	rGO*/GelMA* scaffold	SCs/BM-MSCs	15-mm incision	56
Sun 2023 [113]	Rats	Collagen fibers	UC-MSCs	Spinal cord injury	90
Bydon 2024 [114]	Human	NA	AD-MSCs	Spinal cord injury	672

* HO–PSNCs: Highly oriented poly (L-lactic acid)/soy protein isolate nerve conduits; * PHB: Poly-3-hydroxybutyrate; * rGO: reduced graphene oxide; * GelMA: Methacrylate anhydride gelatin.

Table 2
MSC-based clinical trials for nerve injury and spinal cord injury (SCI).

ClinicalTrials.Gov Identifier	Title	Intervention	Phase(s)/Status/(Start Dates)	Country
NCT02853942	Autologous adipose mesenchymal stem cell transplantation in the treatment of patients with hemifacial spasm	AD-MSCs	Early phase 1 Unknown status (Oct 2016)	China
NCT03336996	Assessment the reconstruction of motor circuits in nerve fiber injuriesafter the treatment of umbilical cord mesenchymal stem cells with blood oxygen level-dependent derived diffusion tensor imaging	UC-MSCs	Not applicable Unknown status (March 2018)	China
NCT04654286	Human amniotic membrane and mesenchymal stem cells composite (BPI + MSCs)	AD-MSCs	Not applicable Unknown status (Nov 2016)	Indonesia
NCT04877067	Therapy of toxic optic neuropathy via combination of stem cells with electromagnetic stimulation (magnovision)	WJ-MSCs	Phase 3 Completed (April 2019)	Turkey
NCT05147701	Safety of cultured allogeneic adult umbilical cord derived mesenchymal stem cells for eye diseases	UC-MSCs	Phase 1 Recruiting (Feb 2022)	Argentina
NCT01920867	Stem cell ophthalmology treatment study (SCOTS)	BM-MSCs	Not applicable Unknown status (Aug 2012)	United States
NCT03011541	This study will evaluate the use of autologous BM-MSCs for the treatment of retinal and optic nerve damage or disease	BM-MSCs	Not applicable Recruiting (Jan 2016)	United States
NCT02482194	Autologous mesenchymal stem cells transplantation for SCI-a phase I clinical study	BM-MSCs	Phase 1 Completed (Jun 2013)	Pakistan
NCT01694927	Autologous MSCs in SCI patients	Autologous MSCs	Phase 2 (Jan 2012)	Chile
NCT02981576	Safety and effectiveness of BM-MSCs vs AT-MSCs in the treatment of SCI patients	AD-MSCs BM-MSCs	Phase 1 Phase 2 Completed (Nov 2016)	Jordan
NCT01676441	Safety and efficacy of autologous MSCs in chronic SCI	BM-MSCs	Phase 2 Phase 3 Terminated (Aug 2008)	Korea
NCT05671796	Autologous BM-MSCs transplantation in patients with subacute SCI	BM-MSCs	Phase 2 Not Recruiting (April 2023)	Brazil
NCT03505034	Intrathecal transplantation of UC-MSCs in patients with late stage of chronic SCI	UC-MSCs	Phase 2 Unknown status (Sep 2019)	China
NCT02152657	Evaluation of autologous MSCs transplantation in chronic SCI: a Pilot study	MSCs	Not applicable Completed (Jan 2015)	Brazil
NCT01446640	MSCs transplantation to patients with SCI (MSCs)	BM-MSCs	Phase 1 Phase 2 Unknown status (Oct 2011)	China
NCT05018793	Safety of cultured autologous adult AD-MSCs intrathecal injection for SCI	AD-MSCs	Phase 1 Suspended (Dec 2021)	Greece
NCT01325103	Autologous BM-MSCs transplantation in patients with SCI	BM-MSCs	Not applicable Completed (July 2010)	Brazil
NCT03521323	Intrathecal transplantation of UC-MSCs in patients with early stage ofcChronic SCI	UC-MSCs	Phase 2 Unknown status (Sep 2019)	China
NCT03521336	Intrathecal transplantation of UC-MSCs in patients with sub-acute SCI	UC-MSCs	Phase 2 Unknown status (Sep 2019)	China
NCT02574585	Autologous MSCs transplantation in thoracolumbar chronic and complete SCI	BM-MSCs	Phase 2 Unknown status (Dec 2019)	Brazil
NCT02574572	Autologous MSCs transplantation in cervical chronic and complete SCI	BM-MSCs	Phase 1 Unknown status (Sep 2017)	Brazil
NCT01909154	Safety study of local administration of autologous BM-MSCs in chronic paraplegia (CME-LEM1)	BM-MSCs	Phase 1 Completed (March 2013)	Spain
NCT02481440	Repeated subarachnoid administrations of hUC-MSCs in treating SCI	UC-MSCs	Phase 1 Phase 2 Completed (March 2018)	China
NCT02688049	NeuroRegen Scaffold™ combined withs stem cells for chronic SCI repair	MSCs	Phase 1 Phase 2 Unknown status (Jan 2016)	China
NCT03308565	Adipose stem cells for traumatic SCI (CELLTOP)	AD-MSCs	Phase 1 Completed (Dec 2017)	United States
NCT01274975	Autologous AD-MSCs transplantation in patient with SCI	AD-MSCs	Phase 1 Completed (July 2009)	NA
NCT02570932	Administration of expanded autologous adult BM-MSCs in established chronic SCI	BM-MSCs	Phase 2 Completed (July 2015)	Spain
NCT01162915	Transfer of BM-MSCs for the treatment of SCI	BM-MSCs	Phase 1 Suspended (July 2010)	United States
NCT01624779	Intrathecal transplantation of autologous AD-MSCs in the patients with SCI	AD-MSCs	Phase 1 Completed (April 2012)	Korea

Table 2 (*continued*)

ClinicalTrials.Gov Identifier	Title	Intervention	Phase(s)/Status/(Start Dates)	Country
NCT01393977	Difference between rehabilitation therapy and stem cells transplantation in patients with SCI in China	UC-MSCs	Phase 2 Unknown status (Jan 2011)	China
NCT05152290	Safety of cultured allogeneic adult UC-MSCs for SCI	UC-MSCs	Phase 1 Recruiting (July 2022)	Argentina
NCT02237547	Safety and feasibility study of cell therapy in treatment of SCI	UC-MSCs	Phase 1 Phase 2 Withdrawn (Sep 2014)	Panama
NCT01769872	Safety and effect of AD-MSCs implantation in patients with SCI	AD-MSCs	Phase 1 Phase 2 Completed (Jan 2013)	Korea
NCT01873547	Different efficacy between rehabilitation therapy and stem cells transplantation in patients with SCI in China (SCI-III)	UC-MSCs	Phase 3 Completed (June 2012)	China
NCT04520373	Autologous AD-MSCs for SCI patients	AD-MSCs	Phase 2 Recruiting (June 2020)	United States
NCT04288934	Treatment of SCI with (AutoBM-MSCs) vs (WJ-MSCs).	BM-MSCs WJ-MSCs	Phase 1 Completed (Aug 2017)	Jordan
NCT02352077	NeuroRegen Scaffold™ with stem cells for chronic SCI repair	MSCs	Phase 1 Unknown status (Jan 2015)	China
NCT03003364	Intrathecal administration of expanded WJ-MSCs in chronic traumatic SCI	WJ-MSCs	Phase 1 Phase 2 Completed (Dec 2016)	Spain
NCT02917291	Safety and preliminary efficacy of FAB117-HC in patients with acute traumatic SCI (SPINE)	AD-MSCs	Phase 1 Phase 2 Unknown status (Dec 2016)	Spain

as 2008, a clinical trial by Geffner et al. (NCT01909154) demonstrated that multiple routes of administration of BM-MSCs were safe and feasible for a wide range of spinal cord injuries, and, on top of that, it provided an advantage in terms of quality-of-life improvement for many patients with spinal cord injuries [115].

Another clinical trial conducted by Yang et al., in 2020 (NCT02481440) accurately assessed neurological recovery by measuring several efficacy metrics and proved that allogeneic hUC-MSCs are safe and effective, dramatically improving neurological dysfunction and restoring quality of life [116]. With this Phase 1/2 trial, it will facilitate the initiation of other prospective, multicenter, randomized, placebo-controlled clinical trials in the future. However, this is not a randomized controlled study, so potentially subject inclusion bias may affect the accuracy of the assessment. In addition, the acquisition of certain efficacy metrics may be affected by the psychological state of the subjects, resulting in some bias in the results. Byson et al.'s group has completed a phase 1 clinical trial also showing that AD-MSCs not only have a favorable safety profile in the treatment of traumatic spinal cord injuries but also improve patients' sensory and motor functions to a certain extent [114]. Additionally, because various nations have their own websites for clinical registration trials, like the Chinese ClinicalTrial Registry (ChiCTR), the UK Biobank, the Japanese UMIN-CTR, India's CTRI, the US ClinicalTrials.gov, etc. In order to increase the sample size and get more comprehensive results, future research may involve clinical registration trials on MSCs' capacity to regenerate neural-related damage across various countries.

The future of MSCs is optimistic due to the outcomes of these clinical studies involving both humans and animals, in addition to the efforts of researchers in this area. However, certain obstacles and restrictions are still existing.

9. Approved MSC therapies for various diseases in different countries

The majority of MSC products that have been approved to be marketed are primarily intended to be utilized in the selection of indications that are based on their two biological properties, which are immune modulation and tissue repair, such as acute graft versus host disease (aGVHD), osteoarthritis of the knee, Crohn's disease, and severe limb ischemia. Currently, there are more than 10 MSC therapies have gained marketing approval in Japan, Canada, India, and Europe.

Until December 18, 2024, the U.S. FDA had not approved any of the MSC therapies to be marketed in the U.S., and remestemcel-L-rknd (Ryoncil, Mesoblast, Inc.) was the first MSCs therapy to be approved by the FDA [117]. Ryoncil was initially approved in Canada and New Zealand in 2012, it was then marketed in Japan for the treatment of aGVHD in children and adults in 2016 and was the first FDA-approved allogeneic BM-MSCs therapy in the U.S. for the treatment of children 2 months of age and younger with steroid-refractory acute graft versus host disease (SR-aGVHD). The official FDA approval of Ryoncil in the United States did not come until December 18, 2024, when it was officially approved by the FDA.

Other MSC therapies that have been approved for marketing in other countries have also held promise for other diseases. Temcell (Prochymal), an allogeneic MSCs product by JCR Pharmaceuticals, received fully approval in September 2015 for the therapy of acute graft-versus-host response (GVHD). The Japanese PMDA conditionally approved Stemirac stem cell therapy in November 2018. Stemirac is a BM-MSCs that was developed by NIPRO CORP, a Japanese company, and it's administered to qualified SCI patients under specialized care. In 2010, the Korea Food and Drug Administration (MFDS/KFDA) approved Queencell, the first MSC-based product, for the treatment of subcutaneous tissue defects. An Indian company known as Stempeutics conducted a phase 4 clinical trial in September 2021, and the results indicated that Stempeucel's allogeneic BM-MSCs product was safe, effective, and had positive, long-lasting effects that not only reduced pain but aided in ulcer healing for severe limb ischemia triggered by Buerger's disease.

And beyond the indications mentioned above, other cell companies in many countries (including Mesoblast, Athersys, Pluristem, Stempeutics, Cynata, etc.) are vigorously exploring new indications for MSC therapies. While there have been no MSC therapies approved for the treatment of neurological injuries to date,

preliminary results from clinical trials have proven their safety and efficacy and, more to the point, have supplied the basis and direction for subsequent trials to move forward.

10. Limitations and further direction

Despite the promising prospects for the development of stem cell therapies in nerve healing following damage, significant optimization of these therapies is required to realize their full potential in the clinical context. The primary issue is the inadequacy of clinical trial data. Several human clinical trial data have showed very limited results compared to expectations, despite the fact that several animal experiments have shown safety and effective results. This could be because human nerve injury varies depending on a number of uncontrollable factors, such as the site and length of the injury, while animal research follows uniform protocols. Another thing worth to note is that no two individuals would experience the identical nerve-related injuries, That's why it's difficult to conduct case-control trials. The effectiveness, safety, and possible potential risks of a therapy product can only be verified via sufficient data from clinical trials.

Additionally, while the transplanted BM-MSCs were efficient, it was difficult to fully control their differentiation, and we cannot rule out the potential that the transplanted BM-MSCs developed into aberrant cells in the spinal cord. Also, it has been reported that MSCs may contribute to tumor growth and metastasis through a variety of mechanisms [118–120]. Primarily, the MSCs may interact with tumor cells by secreting cytokines (e.g., IL-6, IL-8, VEGF, etc.) and exosomes (EVs), which drive tumor cell proliferation, migration, and invasion [121–123]. Further, by inducing epithelial-mesenchymal transition (EMT), MSCs can make tumor cells more aggressive, even by altering the tumor microenvironment [124], enhancing the tumor characteristics such as drug resistance, EMT, and immune escape capabilities of tumor cells. Within the tumor microenvironment, chronic inflammatory signals in tumor tissues and tumor-secreted factors (e.g., TGF-β and Wnt3a) may also drive the transformation of MSCs into a cancer-associated fibroblast (CAFs) phenotype, which provides structural support to the tumor and promotes angiogenesis [125], which further advances tumor growth and metastasis. In spite of MSC's role in promoting tumor progression in some cases, it has also been observed that MSCs can exert anti-tumor effects by inhibiting tumor cell proliferation or promoting apoptosis in tumors [126–128]. Therefore, further research needs to be conducted to figure out the precise mechanism of MSCs in tumors and examine the safety and effectiveness of MSCs in clinical settings in order to fully realize the potential they hold in tumor therapy.

Additionally, research has also evidenced that MSCs from unhealthy donors exhibit extremely limited and unsatisfactory efficacy in clinical settings [129,130], presumably due to the impairments in the proliferative and differentiation capacity of these donor-derived MSCs. The quality of MSCs varies significantly with factors such as the age, gender and health status of the donor, as well as the storage and processing conditions of the MSCs. As high quality MSCs are more likely to achieve the desired therapeutic effects in clinical applications, it is vital to finalize the quality of MSCs in clinical research and applications.

Moreover, the drug management regulations vary by country. Examples include the Japanese Medicines and Medical Devices Administration (PMDA), the Indian Medicines Regulatory Authority (DCGI), the Australian Therapeutic Goods Administration (TGA), the Korean Ministry of Food and Drug Safety (MFDS), the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and the Japanese Medicines Agency (JMA). Since national regulations differ, it is imperative for international organizations to establish standardized policies regarding MSCs, such as the collection, storage, and utilization of the cells. Besides, the market price of MSCs basically ranges from several tens of thousands to more than one hundred thousand US dollars per dose, which is extremely costly, thus the relevant authorities need to regulate the price in the future.

Finally, despite the fact that Schwann cells play an important role in peripheral nerve healing and have a high degree of flexibility, they have not been thoroughly investigated in the setting of acute nerve damage. The involvement of several molecules in neural healing function has a time restriction; more research into the precise mechanisms is required. The insufficiency of stem cells, a decline in growth factor expression, and a slowdown in the production of repair-related Schwann cells are all variables that can lead to the failure of nerve regeneration. Consequently, the way to a deeper understanding of MSCs therapy for the healing of injured nerves must include performing clinical human studies to gather a substantial number of clinical data.

11. Conclusion

In summary, MSCs offer vast promise within the realm of nerve damage and restoration. Their remarkable ability to regenerate, their capacity to shield nerves, and their capacity to reduce inflammation all mark them as hopeful prospects for medical treatments. Harnessing the power of regenerative capacities and optimizing overall outcomes, treatments employing MSCs offer hope to those suffering from nerve injuries. Nevertheless, additional investigation is necessary to comprehensively grasp their operational mechanisms and enhance their clinical utility. By steadfastly delving into new frontiers and pushing boundaries, MSCs could pave the way for a paradigm shift in nerve injury treatment, ultimately enhancing the well-being of individuals.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Ethical approval

Not applicable.

Authors contributions

Conceptualization: Jincheng Zeng, Mingdeng Rong, Ziyu Ye; Writing—original draft preparation: Shuo Song and Cong Li; Writing—review and editing: Ya Xiao; Funding acquisition: Cong Li, Mingdeng Rong and Jincheng Zeng. All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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