Expert Opinion

Stem cells treatment for sciatic nerve injury

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Introduction: Sciatic nerve injury is common and usually results in degeneration of the distal axons and muscle denervation. Chronic muscle atrophy and fibrosis limit the recovery of muscle function and severely compromises efforts to restore muscle function. Despite early diagnosis and modern surgical techniques there is still poor functional recovery.
Areas covered: Stem cell transplantation has been investigated as a promising treatment strategy for peripheral nerve injury, and has demonstrated utility in limiting neuronal damage. The focus has been on the isolation of stem cells from bone-marrow and adipose tissue in addition to embryonic and neuronal stem cells. Transplantation of these cells into transected sciatic nerve in animal models demonstrates clinical improvement, inducing vigorous nerve regeneration accompanied by myelin synthesis. Cell replacement, trophic factor production, extracellular matrix molecule synthesis, guidance, remyelination, microenvironmental stabilization and immune modulation have been postulated as possible mechanisms for stem cell implantation.
Expert opinion: Although further research is still needed, this therapeutic approach will probably become a routine treatment technique in the coming years, especially with bone marrow mesenchymal stem cells. We believe that the most promising results were noted for the use of stem cells of this origin in the treatment of sciatic nerve injury.

Keywords: motor neuron, peripheral nerve injury, sciatic nerve, stem cells

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1. Introduction

1.1 Sciatic nerve injury

The mammalian peripheral nervous system has a limited axonal regeneration capacity following injury [1-3]. Sciatic nerve injury, a common peripheral neuropathy (reported prevalence, 43%) [4], is characterized by muscle weakness, reflex changes and numbness. It can be caused by tumors, cysts or other extraspinal insults. The majority of patients complain of persistent and severe pain, motor dysfunctions and prolonged disability [4,5]. The nature and prognosis remain the same, regardless of the cause of the injury [6,7]. Efforts to restore muscle function are compromised by the fibrosis and scar tissue that occur secondary to muscle-fiber atrophy [8,9] and the slow growth rate (1 – 2 mm/day) of the nerve axon which prolongs muscle reinnervation [10].

1.2 Process of peripheral nerve regeneration

The process of degeneration and consequent regeneration of a peripheral nerve entails a complex sequence of events initiated by Wallerian degeneration of the distal stump, which may or may not favor target-organ reinnervation [11]. The time course varies by species, site of lesion, nerve involved and fiber type [12]. In addition, different types of lesions have different prognoses. In crush lesions, the basal lamina is preserved, generating a propitious environment for regeneration; this is not true

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Article highlights.

- Post-traumatic nerve repair and prevention of muscle atrophy pose major challenges for restorative medicine.
- Stem cells isolated from various origins such as: bone marrow, adipose tissue, amniotic fluid and hair follicles, have demonstrated utility in limiting neuronal damage in a wide variety of experimental neurologic injuries, including stroke, Parkinson's disease, traumatic brain injury, spinal cord injury and peripheral nerve damage.
- Cell replacement, trophic factor production, extracellular matrix molecule synthesis, guidance, remyelination, microenvironmental stabilization and immune modulation have been postulated as possible mechanisms explaining the benefits of stem cell implantation.
- According to the authors' opinion, the most promising results were noted for the use of bone marrow mesenchymal stem cells in the treatment of sciatic nerve injury.
- Further research is needed to determine the optimal stem cell type for peripheral nerve regeneration. This therapeutic approach is undergoing constant development and improvement.

This box summarizes key points contained in the article.

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for transection injury [13]. Successful regeneration may also be impeded by the distance to be covered by the growing nerve fibers [14].

The successful regeneration of peripheral nerve requires the interaction of the extracellular matrix, neurotrophic factors and cellular components. Peripheral nerves are composed primarily of two kinds of cells: axons and Schwann cells. Schwann cells promote neural regeneration by several pathways: increasing the synthesis of cell adhesion molecules; elaborating the basement membrane that contains many cell adhesion molecules and other extracellular matrix proteins (also called neurite outgrowth promoting factors); and producing neurotrophic factors and their receptors. A few days after nerve injury Schwann cells lose myelin. This triggers their activation and proliferation within the distal nerve segment and raises the levels of a variety of neurotrophic factors, cytokines and cell adhesion molecules [15]. Neurite outgrowth promoting factors, either on the cell surface (cell adhesion molecules and recognition molecules) or in the extracellular matrix, promote axonal extension by providing appropriate adhesiveness in the substrate, which facilitates axon-to-axon and axon-to-Schwann cell attachment [11,16].

1.3 Treatment for peripheral nerve injury

Considerable advances have been made in peripheral nerve repair in the last decades. These include the use of epineural or perineural sutures for tension-free repair, and development of techniques of nerve apposition by means of anatomic features. Nevertheless, even with early diagnosis and accurate nerve repair, post-repair function can never reach the pre-injury level. Poor outcome may be the result of many factors, both intrinsic and extrinsic to the nervous system, such as the type and level of injury, presence of an associated injury, timing of surgery and change in the spinal cord neuron and end organ.

Accordingly, researchers are seeking viable alternative approaches [1,9,10,16-19], and attention has recently been addressed to stem cell transplantation. Stem cells are pluripotent or multipotent primitive cells found in most, if not all, multicellular organisms. They have the ability to self-replicate and can differentiate into various cell types of particular tissues [1,5]. Stem cells have demonstrated utility in limiting neuronal damage in a wide variety of experimental neurological injuries, including stroke, Parkinson's disease, traumatic brain injury, spinal cord injury and peripheral nerve damage [20]. The mechanism(s) underlying the beneficial effect of implanted stem cells from various sources on peripheral nerve regeneration remain unclear. Suggestions include cell replacement, trophic factor production, extracellular matrix molecule synthesis, guidance, remyelination, microenvironmental stabilization and immune modulation [1,7,18,19,21-24].

This review focuses on the question of the optimal stem cell source for the treatment of sciatic nerve injury.

2. Stem-cell-based treatment of peripheral nerve injury

2.1 Embryonic stem cells

Embryonic stem cells are pluripotent stem cells derived from the inner cell mass of blastocysts. They can differentiate into various neuronal cell types, including astrocytes and oligodendrocytes. The neural phenotypes of *in vitro*-differentiated embryonic stem cells closely resemble those of the equivalent mature cells *in vivo*. Deshpande *et al.* [25] claim that embryonic stem cells transplanted into the spinal cord in an animal model were able to differentiate into relatively normal motor neurons, extend axons into peripheral nerves, form new neuromuscular junctions with denervated muscles, and delay muscle atrophy caused by nerve injury [25], with improvement in gait. In two separate studies, Erb *et al.* [26] and Thomas *et al.* [27] proved that the transplantation of embryonic precursor cells into the peripheral nerve of adult rats effectively arrested muscle atrophy when there were no regenerating peripheral axons from the proximal nerve stump. The transplanted precursor cells differentiated into neurons that expressed motor neuron markers. These cells extended axons into the muscle and formed cholinergic terminals. Thereafter, Craff *et al.* [8], showed that direct transplantation of embryonic-stem-cell-derived motor neuron progenitors into denervated muscle helped to prevent muscle atrophy in an adult rat model of peripheral nerve injury.

However, using embryonic stem cells in peripheral nerve therapy poses several problems: their acquisition and manipulation raises ethical issues, and the cells can be tumorigenic (leading to formation of teratomas). In addition, because embryonic stem cells are not autologous, their transplantation

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must be accompanied by immunosuppressive treatment to prevent rejection.

2.2 Neural stem cells

Neural stem cells (NSCs) are widely distributed in the embryonic CNS and mainly located in the hippocampus and subventricular zone in the fetal and adult CNS. The therapeutic potential of neural stem cell transplantation in peripheral nerve injuries is supported by several recent studies of neural stem cell differentiation. Murakami *et al.* [17] reported evidence of nerve regeneration after bridging a sciatic nerve defect with a collagen tube filled with neural progenitor cells. The cells were able to differentiate into Schwann-cell-like cells and survived for up to 2 months. MacDonald [28] reported that functional motor neurons could be differentiated from mouse multipotent spinal cord precursor cells in culture and after transplantation into a transected peripheral nerve. The differentiated neurons expressed motor neuron markers of cholineacetyltransferase and extended axons into the muscle, where they formed cholinergic terminals. Using a rat model, Gao *et al.* [29] engrafted primed human neural stem cells differentiated into motoneurons into the ventral horn of the spinal cord following sciatic nerve crushing. The neurons received putative synapses and emitted large cholinergic and myelinated axons which traveled through the ventral roots and sciatic nerves to the periphery, where they made presynaptic contact with medial gastrocnemius muscle cells. Neurobehaviorally, there was an improvement in electromyography and gait parameters. Some of the transplanted cells seemed to develop into functional motor neurons that were partially integrated into the spinal and peripheral circuitry [29]. More recently, Gu *et al.* [10] investigated the ability of transplanted fetal neural stem cells to arrest the atrophy of denervated muscle and the primary mechanism responsible for this effect. They found that the transplanted stem cells differentiated into neurons in peripheral nerves that synthesized and secreted synaptophysin, suggesting high neuron activity. Retrograde tracing and electromyography analysis demonstrated an established and functional pathway between the target tissues and the transplanted fetal neural stem cells [10].

2.3 Amniotic fluid stem cells

Amniotic fluid appears to be a novel source of stem cells for therapeutic transplantation. Amniotic-fluid-derived stem cells have characteristics of both mesenchymal and neural stem cells. Interestingly, amniotic fluid was shown to contain cells expressing the octomer binding factor 4 (Oct-4) antigen, a specific marker of pluripotent stem cells, which displayed multilineage differentiation potential: depending on the specific culture conditions, they differentiated into adipocytes, osteocytes or neuronal cells. These findings are important because the use of amniotic fluid stem cells does not raise ethical concerns [18,19,23].

Pan *et al.* [16] demonstrated that transplanted human amniotic fluid stem cells augmented nerve regeneration across a sciatic nerve gap, although the underlying mechanism was not fully understood. In a later study, the same group [18] found that rat amniotic stem cells transplanted around a crushed sciatic nerve increased nerve regeneration, as manifested by an increase in motor function, improved electrophysiology results and increased myelination. However, the percentage cell survival in the transplanted tissue was low, and again, no clear mechanism was established. The authors also found that the administration of amniotic fluid stem cells combined with G-CSF, an anti-inflammatory and anti-apoptotic agent, decreased inflammatory cell infiltration and attenuated the elevated production of inflammatory cytokines, significantly augmenting peripheral nerve repair. They attributed the effect of the combined treatment to the decreased production of cytotoxic inflammatory mediators and increased the survival of implanted stem cells owing to G-CSF modulation [18]. Peripheral nerve regeneration was also enhanced when amniotic fluid stem cell transplantation was combined with hyperbaric oxygen (HBO), which exerts anti-apoptotic and anti-inflammatory effects [19], or with fermented soybean extracts (Natto), which rescued a significant number of stem cells from apoptosis [22].

Cheng *et al.* [23] showed genetically modified amniotic fluid stem cells to overexpress glial-cell-derived neutrotrophic factor (GDNF) and transplanted them into a rat model of sciatic nerve injury. The modified cells not only induced a significant improvement in neurobehavior, they also promoted nerve regeneration, as evidenced by a decrease in Schwann cell apoptosis and in vacuole counts. The mechanisms suggested to explain the effect included immunomodulation, secretion of neurotrophic factors, and integration, as part of the host nerve tissue [24].

2.4 Bone marrow mesenchymal stem cells

Bone marrow mesenchymal stem cells (marrow stromal cells) normally provide structural and functional support for hemopoiesis [30]. They are easily accessible through bone marrow aspiration, present no ethical problems, and can be readily expanded on a large scale for autotransplantation. They are known to have the potential to differentiate into bone, cartilage, and fat tissue [15]. Bone marrow mesenchymal stem cells also express neural markers [31] and were found to have therapeutic benefit in various animal models of neurodegenerative disorders, such as Parkinson's disease, multiple sclerosis and stroke [30,32-34]. In addition, the stem cells can be induced to differentiate into neuronal cell types, such as Schwann cells.

In the study of Goel *et al.* [1], bone-marrow-derived mononuclear cells transplanted directly between the ends of a transected sciatic nerve increased the rate and degree of nerve regeneration. The transplanted cells facilitated the process of myelin formation (in terms of both percentage of myelinated fibers and thickness of the myelin rings) and axon regeneration and decreased the incidence of degenerative changes. The authors suggested that this effect may be due to stem-cell expression of trophic factors, leading to axonal growth and to differentiation of the stem cells into Schwann-like cells, leading to myelin reformation.

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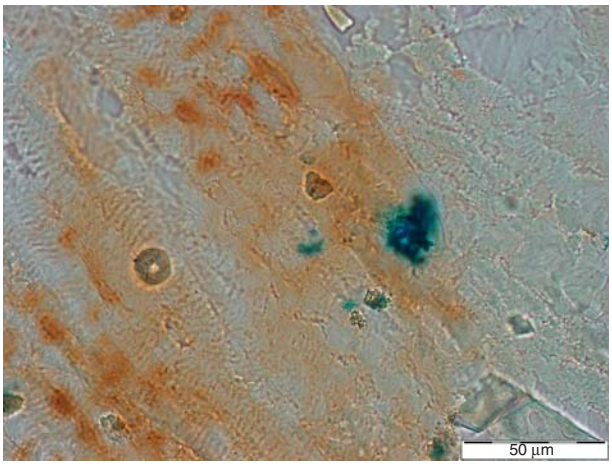

Figure 1. Demonstrative immunostaining of transplanted bone marrow mesenchymal stem cells induced to secrete neurotrophic factors in the injured rats' muscle. Three weeks after transplantation, the cells can be detected in the transplanted tissue, surrounding the injured sciatic nerve. The cells were prelabaled with iron and stained with Prussian blue. The brown color indicates on the presence of secreted BDNF (for more details, see [38]).

Dezawa *et al.* [20], transplanted Schwann cells derived from bone marrow mesenchymal stem cells into the transected sciatic nerve of adult rats. The results revealed vigorous nerve regeneration accompanied by myelin synthesis. The authors suggested that bone marrow mesenchymal stem cells can differentiate into myelinating cells capable of supporting nerve fiber regrowth and therefore may be used therapeutically to induce nerve regeneration. Their findings were supported by Mimura *et al.* [35] in a similar study. Others also concluded that bone marrow mesenchymal stem cells are capable of differentiating into Schwann cell-like cells both *in vivo* and *in vitro* and induce myelination of regenerated nerve fibers after sciatic nerve injury [15,36,37].

Dadon *et al.* [38] successfully converted bone-marrow-derived mesenchymal stem cells into astrocyte-like cells, with the typical astrocyte cell morphology and expressing typical astrocyte markers, which produced and secreted high levels of neurotrophic factors (NTF^+ cells) such as brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF, **Figure 1**). Injection of these cells into rats one day after sciatic nerve crush was associated with marked preservation of motor function, maintenance of myelinated motor axons, and significant inhibition of degeneration at the neuromuscular junctions [38].

2.5 Adipose stem cells

Adipose tissue is an abundant source of postnatal stem cells. Adipose stem cells are available in abundance, may be harvested with minimally invasive techniques associated with low morbidity and have convenient phenotypic and gene-expression profiles as well as favorable culture and expansion properties. These features make adipose tissue a very promising source of stem cells for tissue regeneration [39]. In addition to their multipotent differentiation ability, adipose stem cells secrete a variety of growth factors and cytokines that may positively influence axonal regeneration. Erba *et al.* [39] showed that adipose stem cells improve peripheral nerve regeneration *in vivo* by providing a protective environment for the distal nerve end where the bulk of Schwann cell migration into the conduit takes place. In the study by Santiago *et al.* [7], adipose stem cells transplanted into a an animal model of peripheral nerve injury induced the formation of a thicker nerve and modestly decreased muscle atrophy. The cells survived for up to 12 weeks in the injured nerve. However, functional recovery was not observed, indicating that proper nerve reinnervation of the leg and toes had not occurred [7]. di Summa *et al.* [40] seeded adipose tissue stem cells or bone marrow mesenchymal stem cells in fibrin conduits to repair sciatic nerve injury. Both cell populations equally supported axonal regeneration. Nevertheless, the authors preferred the adipose stem cells for future clinical use because they were easier to isolate. Humans have abundant subcutaneous fat deposits, such that adipose stem cells can be isolated in large quantities by conventional liposuction under local anesthesia. This avoids the discomfort and tissue morbidity associated with bone marrow aspiration, giving adipose stem cells a potential advantage for tissue engineering applications [40].

2.6 Hair stem cells

Hair follicles contain an abundance of actively growing pluripotent stem cells that can differentiate into neurons, glia, keratinocytes, smooth muscle cells and melanocytes *in vitro*. They have the important advantages of low malignant potential, avoidance of immunologic rejection and no ethical issues. Hoffman [41] reported that hair follicle stem cells differentiated into blood vessels and neural tissue after transplantation into the subcutis of nude mice. Amoh *et al.* [42] showed that nestin-expressing hair follicles cells, which are abundant in the bulge area, enhanced the rate of nerve regeneration and the restoration of nerve function after transplanting them into a gap region of an injured sciatic nerve. Amoh *et al.* [43] also reported that direct transplantation of hair follicle stem cells into an injured peripheral nerve in mice greatly enhanced the rate of nerve regeneration and the restoration of nerve function. The cells differentiated into Schwann cells and apparently promoted the growth of pre-existing axons [21,43]. However, the generation, purification and identification of hair follicle stem cells remain problematic.

2.7 Skin stem cells

The dermis contains neural-crest-related precursor cells, termed skin-derived precursors, that can differentiate *in vitro* into neural-crest-cell types, including those with characteristics of peripheral neurons and Schwann cells. Skin-derived precursors have been generated in the neonatal

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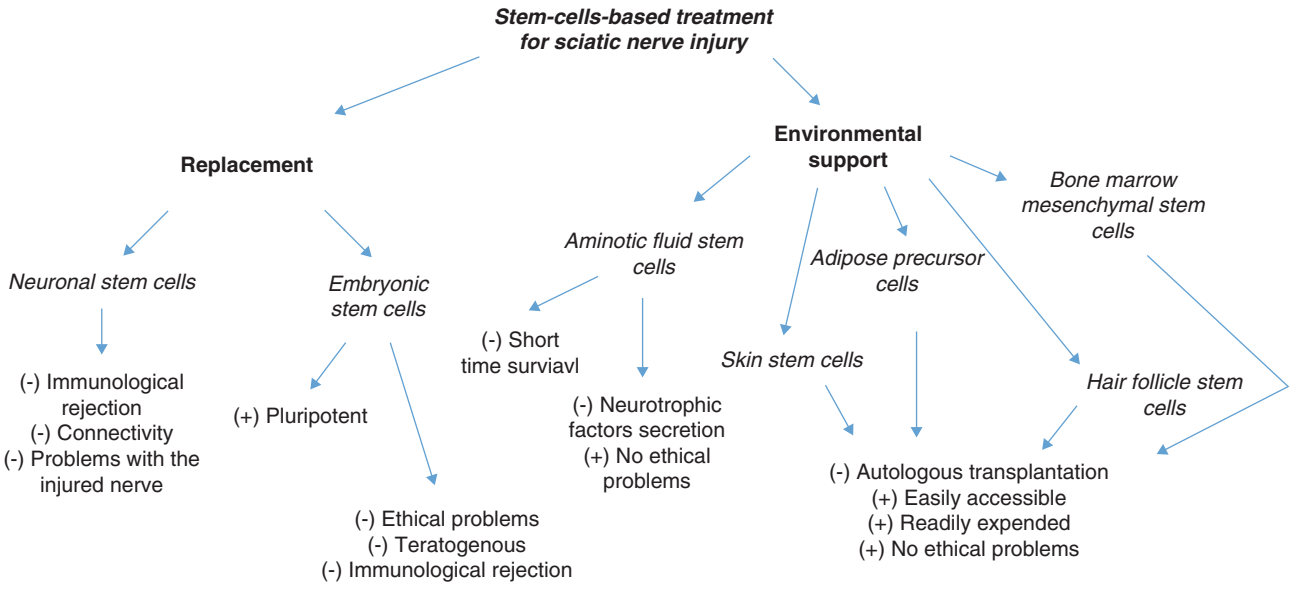

Figure 2. Approaches of stem cells based treatment for sciatic nerve injury. Cellular replacement and environmental support are the two main therapeutic approaches of stem-cell-based treatment for peripheral nerve injury. Different types of stem cells are being studied in order to find the optimal stem cells source to treat the problem.

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and adult skin of both rodents and humans in response to environmental cues. When cultured with neuregulin-1, an agent that promotes the proliferation and differentiation of Schwann cells from embryonic neural crest precursors, rodent and human skin-derived precursors exhibited a Schwann-cell-like phenotype, characterized by the generation of bipolar S100-positive cells that co-expressed myelin basic protein, glial fibrillary acidic protein and p75 neurotrophin receptor, known to stimulate peripheral nerve regeneration [44,45]. Following transplantation into acellular (freeze-thawed) isografts, the Schwann-cell-derived cells survived, migrated and maintained the expression of Schwann cell markers for at least 8 weeks. Already after 4 weeks, they induced axonal regeneration, myelination, and electrophysiological recovery [44,45].

3. Conclusions

Posttraumatic nerve repair and prevention of muscle atrophy pose major challenges for restorative medicine [9]. Several approaches have been proposed to exert beneficial effects on peripheral nerve regeneration, such as the application of an electric field, nerve autografts, administration of neurotrophic factors etc. In the past few years accumulating data have indicated that stem cell implantation exerts favorable effects on peripheral nerve regeneration. Cell replacement, trophic factor production, extracellular matrix molecule synthesis, guidance, remyelination, microenvironmental stabilization, and immune modulation have been postulated as possible mechanisms for stem cell implantation [2,3].

Recent studies have shown that the transplantation of stem cells of different origins has favorable effects on posttraumatic neural regeneration *in vitro* and *in vivo* (**Figure 2**). These findings have important implications for the treatment of sciatic nerve injury. Further studies are needed to discern the mechanism(s) underlying these effects.

4. Expert opinion

Stem-cell-based therapy has the potential to induce neural regeneration after sciatic nerve injury. Several groups have turned their attention to identifying accessible sources of stem cells for therapeutic transplantation. Emphasis has been placed on cells that are easily accessible, rapidly expandable in culture and capable of surviving and of integrating into the host tissue. Stem cells have so far been isolated from bone marrow, adipose tissue, amniotic fluid and hair follicles, among others.

In one stem-cell-based therapeutic approach, neural stem cells are transplanted into the lesion site in order to replenish the damaged neurons. However, problems include the connectivity between the injured nerve and the transplanted cells and the possible need for immunosuppression to prevent rejection. The use of embryonic stem cells instead of neural stem cells was associated with favorable peripheral nerve regeneration, but it too is hindered by ethical questions, the problem of immunological rejection and risk of tumor formation.

Recent studies have demonstrated the reprogramming of fibroblasts to a pluripotent state. The use of autologous induced pluripotent stem cells (iPSCs) could overcome the

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obstacles of immune rejection and ethical issues. These cells have been differentiated into motor neurons and astrocytes as a possible therapeutic approach for motor neuron disorders such as spinal cord injury and amyotrophic lateral sclerosis [46,47]. Although there are no reports yet, we believe that in the near future theses cells will be investigated also as a therapeutic approach for sciatic nerve injury.

A second stem-cell-based therapeutic approach involves the transplantation of stem cells into the surrounding tissue of the injured nerve in order to improve its environment. This method was tested with adipose tissue stem cells, which harbor the potential to improve peripheral nerve injury by their inherited neurotrophic factor secretion. However, they were found to survive only for a short term after transplantation.

Another highly investigated stem cell source is the bone marrow. These cells aid functional and structural aspects of nerve regeneration. Bone marrow mesenchymal stem cells are easily accessible and do not create teratomas, and their use circumvents ethical problems. Several studies tried to differentiate bone marrow mesenchymal stem cells into various neural cell types, such as Schwann cells, to ehance their beneficial effect on nerve regeneration. Overall, promising results were noted for the use of bone marrow mesenchymal stem cells in the treatment of sciatic nerve injury.

Adipose tissue and hair cells also provide an effective, accessible, autologous source of stem cells for the treatment of peripheral nerve injury, with no ethical problems. Additionally, the cells can be expanded in culture after isolation [43].

Further research is needed to determine the optimal stem cell type for peripheral nerve regeneration. This therapeutic approach is undergoing constant development and improvement. We believe stem cell therapy will ultimately become routine in patients with sciatic nerve injury.

Declaration of interests

D Offen and E Melamed are consultants for Brainstorm Cell Therapeutics (Israel). The other authors have no conflicts of interest to declare and no funding has been received in preparation of the manuscript.

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