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Bone Marrow-Derived Cells and Peripheral Nerve Injury: Translational Implications for Pain and Regeneration Treatments

Vanina Usach[1*], Florencia Coronel[2], Mariana Malet[3], Gonzalo Piñero[1], Candelaria Leiguarda[3], Mailín Casadei[3], Marcelo Villar[3], Patricia Setton-Avruj[1*], Pablo Brumovsky[3*]

[1]Departamento de Química Biológica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires. Instituto de Química y Fisicoquímica Biológicas, Dr. Alejandro Paladini (IQUIFIB), UBA-CONICET, Buenos Aires. Argentina.

[2]Laboratorio de Nocicepción y Dolor Neuropático, Instituto de Biología y Medicina Experimental – CONICET, Vuelta de Obligado 2490, C1428ADN, Buenos Aires, Argentina.

[3]Instituto de Investigaciones en Medicina Traslacional (IIMT), Universidad Austral-CONICET, Facultad de Ciencias Biomédicas, Universidad Austral, Buenos Aires, Argentina.

Abstract

Traumatic injury of peripheral nerves is a serious concern for both patients and clinicians, and is commonly associated to neuropathic pain and complete or partial loss of functionality of the affected limb. Stem cell therapy has emerged as a promising tool to improve the outcome of patients with peripheral nerve injury, and an increasing number of pre-clinical and clinical studies are adding support towards their use in humans. In the present review, we will address specifically the participation of bone marrow stromal cells (BMSC; including a group of multipotent adult progenitor cells (MAP)) and bone marrow mononuclear cells (BMMC, a heterogeneous fraction that contains BMSC populations, among others), both of endogenous origin or exogenously transplanted, for the control of pain and the improvement of regeneration. We will describe the state-of-the-art knowledge on the cellular and molecular mechanisms involved in the action of BMSC and BMMC during traumatic injury of nerves. Finally, we will address the translational implications that may eventually lead to therapeutic options for humans.

Keywords: *Allodynia; Bone Marrow; Hyperalgesia; Mesenchymal Stem Cells; Neuropathic Pain; Peripheral Nerve Injury; Regeneration*

Abbreviations: BMMC: Bone Marrow Mononuclear Cells; BMSCs: Bone Marrow Stromal Cells; CCI: Chronic constriction injury; CNS: Central Nervous System; DRGs: Dorsal Root Ganglia; GAL: Galanin; HSC: Hematopoietic Stem Cells; IL: Interleukin; IFNγ: Interferon Gamma; MBP: Myelin Binding Protein; MCP-1α: Monocyte chemo attractant protein-1α; MNC: Mononuclear cells; MNC-H: Hematopoietic Mononuclear Cells; MSC: Mesenchyme Stem Cells; NPY: Neuropeptide Tyrosine; PNS: Peripheral Nervous System; p75NTR: Neurotropic Factor p75; CS: Schwann Cells; SDF-1: Stromal cell-derived factor-1; SNI: Spared Nerve Injury; TGFβ1: Transforming growth factor beta 1; WD: Waller Ian Degeneration.

Introduction

In the United States and Europe alone, 100.000 patients receive surgery due to peripheral nerve injury, causing 150.000 billion dollars in estimated costs, of which 87% represent lost productivity [1-2]. Peripheral nerve injury leads to two debilitating situations: 1) neuropathic pain and 2) alterations in motor control; autonomic symptoms can also be present when autonomic nerves are injured (https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Peripheral-Neuropathy-Fact-Sheet). Typical manifestations of neuropathic pain are allodynia (painful sensations in humans or pain-like behavior in animals, elicited by a mechanical or thermal stimulus that normally does not cause pain) and hyperalgesia (an increased pain response produced by a stimulus that normally causes pain in humans or pain-like behavior in animals) [3]. Motor control of striated muscles is also severely compromised during peripheral nerve injury, with recovery being highly dependent both in the efficiency as well as the speed at which regeneration of the injured nerves occurs [1]. The mechanistic analysis of peripheral nerve injury, regeneration and neuropathic pain in humans is of high complexity. However, several animal models have been developed (see [4]) in order to expand our knowledge about the molecular and cellular mechanisms underlying the mentioned conditions and to develop potential new pharmacological therapies (see [1, 5]).

Wallerian degeneration during peripheral nerve injury

The basic structure of peripheral nerves includes two main components: axons and Schwann cells (SC), the latter involved in the synthesis of the myelin sheet surrounding myelinated nerves [6]. Mechanical injury of peripheral nerves, for example, due to axotomy or intense compression, commonly leads to nerve degeneration, first

***Address for Correspondence:** Dr. Pablo R. Brumovsky, Instituto de Investigaciones en Medicina Traslacional (IIMT), Universidad Austral-CONICET, Facultad de Ciencias Biomédicas, Universidad Austral. Av. Juan D. Perón 1500, Derqui, Pilar, B1629 AHJ, Buenos Aires, Argentina, Tel: +54 0230 448 2699; E-mail: pbrumovs@austral.edu.ar

***Address for Correspondence:** Dr. Patricia Setton-Avruj, Departamento de Química Biológica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires. Instituto de Química y Fisicoquímica Biológicas, Dr. Alejandro Paladini (IQUIFIB), UBA-CONICET, Buenos Aires. Argentina, Tel: +5411 4964 8287; E-mail: setton@qb.ffyb.uba.ar

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at the injured site and later also distally. Such degenerative event is typically called Wallerian degeneration (WD), a pathophysiological process characterized by loss of contact between the axon and the SC, as well as degeneration of the damaged nerve fibres. In the presence of a transient injury (acute nerve compression), the process above is followed by SC proliferation, demyelination, and subsequent axonal regeneration and remyelination [7-10].

WD typically results in protein reorganization, with the appearance of immunoreactive clustering of myelin basic protein (MBP) and P0 – two proteins characteristic of myelin - in the distal end of the damaged nerve [11-12]. WD also involves the dissolution of microtubules, rupture of neurofilament networks and changes in the phenotype of SC in myelinated axons. Interestingly, damaged SCs appear to differentiate into a pre-myelinating stage that allows them to proliferate once again [13]. These "activated" SC can also change their functional capacities, dissolving their myelin and behaving as phagocytes [13].

The axonal destruction and removal of myelin during WD requires a full inflammatory response to be complete, which is reflected by the heavy invasion of macrophages within the bloodstream during the first 3-5 days after the injury [14-16]. This also leads to spontaneous migration of macrophages and non-differentiated cells from the bone marrow (CD34+) to proximal and distal portions of the damaged nerve, the later confirmed as bone marrow mononuclear cells (BMMC) by their expression of α-globin mRNA [12]. Macrophages participate in the remyelination process through phagocytic cleansing of myelin debris [17-18] as well as by release of trophic factors that influence nerve repair [19-21]. On the other hand, non-differentiated cells from bone marrow are believed to participate in the repair of injured nerves by, for example, differentiation into neuronal [22-25] or SCs [22].

It is relevant to mention that the nerves affected by WD express a series of cytokines and chemokines, including interleukin (IL)-1β, IL-6, gamma interferon (IFNγ), tumoral necrotic factor alpha (TNF-α), monocyte chemo attractant protein 1 alpha (MCP-1α) and the macrophage inflammatory protein 1 alpha (MIP-1α) [21, 26]. These molecules contribute to the coordination of inflammatory cellular traffic and axonal and myelin degradation, capable of acting as trophic factors for new axons. SCs from the distal stump also produce a great variety of neurotrophic factors and cytokines, adhesion molecules and extracellular proteins, also contributing to axonal regeneration [27-29].

Current strategies for the treatment of neuropathic pain and the improvement of nerve regeneration

Pharmacological strategies

The Neuropathic Pain Special Interest Group (NeuPSIG) from the International Association for the Study of Pain (IASP) has issued guidelines based on clinical evidence for the pharmacological management of neuropathic pain, taking into account efficiency, adverse effects, life quality impact, convenience and costs involved. Thus, based on a lengthy analysis of tenths of clinical trials, the medications that are recommended in the mentioned guidelines as a first line treatment of neuropathic pain include tricyclic antidepressants (amitryptiline, imipramine, clomipramine), serotonin-noradrenaline reuptake inhibitors (duloxetine and venlafaxine), and calcium channel ligands α2-δ (eg. gabapentin and pregabalin). As second line treatment, tramadol, capsaicin and lidocaine patches are recommended (although opioid-based medication can also be used as the first line in certain clinical circumstances). The drugs that could be used as a third line treatment include botulinum toxin A and strong opioids [30-32].

Despite the existence of such grading methods, neuropathic pain treatment is complex; it is estimated that only 50% of affected patients respond with partial relief [33]. Exacerbating the situation, the majority of the analgesics currently prescribed cause some type of adverse effect, limiting their use in high doses or for long periods of time [34].

Finally, there is currently no clinically available pharmacologic approach that can efficiently restore damaged nerves, even though a number of molecules including peptides, growth factors, hormones and immune suppressants are being studied at the preclinical level (see [1, 35]).

Interventionist strategies

There are some conditions under which pain becomes refractory and no longer responds to treatment. For this type of patients, other kinds of therapies are applied: epidural blockade with local analgesics and steroids, sympathetic blockade, or radiofrequency treatment for herpes zoster or spinal radiculopathies [36-37]. The intrathecal administration of drugs can be useful for the refractory pain handling, optimizing patient's functionality and minimizing the use of systemic drugs [38]. Currently, morphine and ziconotide are the two most widely used drugs for intrathecal, long-term administration, approved by the Food and Drug Administration (FDA).

Concerning nerve repair, a direct intervention using epineural micro-sutures is the surgical treatment of choice, but only in conditions of tension-free coaptation and good vascularization. Otherwise, nerve grafts are used to account for significant gaps between the proximal and distal nerve stumps. Alternatively, nerve transfers (use of a healthy nerve to reconnect the distal stump of a relevant damaged nerve) or nerve conduits (use of biological or synthetic nerve guidance channels), sometimes with luminal additives (e.g. neurotrophic factors) can be used in a select number of clinical situations. However, the challenge remains, as in many cases, patients treated as described above show only partial recovery (see [1, 39]). Finally, a number of experimental strategies including the so-called electroceuticals (delivery of electrical impulses), fat grafting and optogenetics are being intensely evaluated using animal models [2].

Cell therapy strategies

Transplant of diverse types of cells for the improvement of functional and morphological recovery of damaged nerves is one of the most recent developments in search of options for pain treatment and regeneration [1]. In the following sections, these approaches will be addressed in detail, particularly concerning peripheral nerve injury, and the evolution of the concept of cell transplantation of different types of cells.

The use of cultured Schwann cells for the repair of damaged peripheral nerves

It is known that the central nervous system (CNS) has restricted possibilities for self-healing [40]. Even though neural stem cells are present in the adult, their ability to generate new functional neurons in response to neural damage is limited [40]. In contrast and as previously mentioned, axonal regeneration does occur in the peripheral nervous system (PNS), in great part thanks to the occurrence of WD and the accompanying proliferation and activation of SC [9-10]. In

fact, Hall described that SC derived from the distal segment of a nerve damaged by axotomy or compression are essential for the myelination of regenerated axons [9].

The observations above led to the early proposal of SC transplantation for the treatment of damaged peripheral nerves. In fact, even though it has been observed that the PNS is able to self-regenerate when it is provided with an artificial graft composed of non-cellular substances like type I collagen or alginate [41-43], such capacity is enhanced by the additional presence of SC or SC-like cells (induced MSCs). In support, several studies have shown that SC transplantation delays cell death, prevents axonal degeneration [44-45], promotes remyelination and increases the conduction of action potentials through regenerated nerves [22-24, 46-49]. However, drawbacks in the application of such therapy in the clinical setting include: 1) the fact that, to obtain SC for autologous transplant, another healthy nerve should be sacrificed [50], 2) the low yields of SC isolation [50-52] and 3) the need for significantly lengthy cell culture techniques to obtain an optimal number of SC, making them less appealing in the context of emergency due to trauma.

The emergence of stem cells for transplantation

The limitations in the use of SC for transplantation led to the search for and characterization of some other type of cell that, in addition to promoting remyelination, was multipotent and readily available, could proliferate *in vitro*, and could easily integrate into the receptor tissue [50-56]. With such objectives in mind, embryonic stem cells emerged as an interesting option, particularly because of their capacity to differentiate into a multiplicity of phenotypes, including neural ones [40, 50, 57-61]. However, the significant restrictions hindering the use of embryonic cells for transplantation in humans, which include ethical concerns, their viability, purity and carcinogenic potential, promoted the emergence of other sources of adult multipotent cells that stimulated neural regeneration in different experimental models of nerve injury.

The effort led to the identification of a number of adult multipotent cells such as bone marrow mesenchymal stem cells [62], olfactory ensheathing cells [63-64], endothelial precursors [65], adipocyte mesenchymal stem cells [66-68], dental pulp stem cells [69], and skin-derived precursor stem cells [70]. Stem cells offer a multipotent cell source for the replacement of damaged or dead cells/neurons, and represent a pathway for the release of trophic factors to injured nerves and neurons [71]. Although the disadvantages and uncertainties regarding the application of pluri- or multipotent cells are still many, the possibilities and advantages offered by this type of treatment are truly fascinating: nothing more and nothing less than tissue repair [40, 58, 61, 72-74].

Of the various stem cells studied thus far, two have gained attention in the last two decades, as suitable for performing autologous transplants: 1) Bone marrow stromal cells (BMSC) and 2) bone marrow mononuclear cells (BMMC).

Presenting BMSC and BMMC

BMSC

Two different populations of multipotent adult stem cells have been identified in bone marrow: hematopoietic (HSC) and mesenchymal (MSC) stem cells [58, 75]. MSC represent around 0.001% of the total cells found in the bone marrow and are in charge of creating the adequate microenvironment for renewal, proliferation and differenti-ation of hematopoietic cells [75-76]. MSC give rise to stromal cells (fibroblasts, adipocytes and vascular endothelial cells), chondrocytes, osteocytes and smooth muscle cells [58, 75]. MSC cannot only differentiate and dedifferentiate, but they can also transdifferentiate into cells types different from the mesenchymal lineage [57-58, 60]. So far, it has been demonstrated that they are capable of giving rise to cardiomyocytes [77], hepatocytes [78], neurons [79-80] and SC [24].

HSC and MSC from bone marrow can be easily separated in culture, as HSC remain in the suspension while MSC adhere to the plastic used for cell culturing [58, 75]. The cells attached are also known as BMSC and include a population with high plasticity that give place to multipotent adult progenitors (MAPs), stromal progenitors and mature stromal cells.

Another relevant feature of BMSC is their ability to migrate and implant in the nervous system, as it has been demonstrated by the identification of labeled BMSC in the brain of irradiated mice receiving systemic infusion of such cells [81]. Moreover, it has been demonstrated that BMSC actively participate in regeneration processes of the central nervous system (CNS), promoting a functional recovery in animals with different types of neurological damage [82-89]. Interestingly, once BMSC are installed in the damaged brain, they begin to express neuronal (NeuN) and astrocytic markers (glial fibrilar acidic protein (GFAP)) [89]. Altogether, these characteristics of BMSC highlighted their potential for the development of strategies in tissue repair therapy, including the nervous system [58, 72, 74] [Table I].

BMMC

BMMC, also obtained from bone marrow samples, comprise a heterogeneous cellular fraction including BMSC, HSC [90], hematopoietic precursors and endothelial cells [91]. This heterogeneity has led some authors to question the use of BMMC. However, it is well known that BMSC are susceptible to phenotypic rearrangements in culture, meaning that the populations obtained for different transplants are not necessarily homogenous [92]. In contrast, it has been proposed that there is a synergistic interaction between the stromal and non-stromal components of BMMC, which may optimize their regenerating capacity in damaged nerves [93]. Hence BMMC have recently become the focus of attention, not only for their easy production, but also because they do not require passage through culturing protocols for their expansion and/or differentiation, therefore bypassing phenotypical rearrangements that can occur when handling BMSC [92].

BMMC promote angiogenesis, neuroprotection and neuroregeneration as it was observed in various rodent models of CNS [94-96] and PNS injury [97]. Also, it has been demonstrated that BMMC differentiate into hepatocytes in animal models with hepatic damage [98], and that they can also differentiate into cardiomyocytes or contribute to the reduction of inflammation in the context of cardiac infarction [99-100]. Finally, BMMC produce numerous cytokines and trophic factors that delay cell death [101-102] and promote the recovery of several types of damaged tissue [91, 103-104] [Table I].

Influence of BMSC and BMMC on neuropathic pain

Coronel et al. [105] first showed that systemic injection of BMSC in rats with sciatic nerve crush results in a very clear mechanical and thermal antiallodynic effect. Moreover, they demonstrated that the effect was positive both in preventive and ameliorating fashions [105]. Importantly, the administration of vehicle or other population of marrow derived cells (hematopoietic mononuclear cells (MNC-H)) failed to exert the antiallodynic effects, indicating that the ability to attenuate pain was inherent of BMSC [105]. Further supporting their antiallodynic role, it was later shown that systemic injection of BMSC

Table I: Comparison between BMSC and BMMC

	BMSC	BMMC
Cell population	*Homogeneous*	*Heterogeneous*
Readiness for transplant	*Several weeks*	*1-2 hours*
Availability	*Culture need for expansion*	*Fresh isolation*
Phenotype rearrangements	*Possible to occur after culture*	*Not demonstrated*
Type of transplant	*Autologous possible after culture*	*Autologous*
Migration capacity	*Yes*	*Yes*
Transdifferentiation potential	*Yes*	*Yes*
Regeneration potential	*Yes*	*Yes*
Effect on pain	*Positive*	*Positive*
Multipotency	*Conserved*	*Partially conserved*

in rats with chronic infraorbital nerve compression or ligation of the tendon of the anterior superficial part of the masseter muscle results in long-term attenuation of mechanical hypersensitivity and allodynia [106]. Moreover, systemic injection of human BMSC in mice with a selective injury of the tibial and common peroneal branches of the sciatic nerve (also called spared nerve injury or SNI) has been shown to reduce thermal and mechanical allodynia [107].

Local application of BMSC has also been shown effective in modulating neuropathic pain. Thus, intra-ganglionar administration of BMSC in rats with single ligature nerve constriction, results in a clear antiallodynic effect [108]. Also, both ipsilateral intramuscular [106] and intrathecal administration [109] of BMSC in rats with ligation of the masseter muscle tendon [106] or mice with chronic constriction injury (CCI) or SNI of the sciatic nerve [109], results in a prolonged decrease in mechanical and thermal hypersensitivity. Interestingly, the intrathecal effects of BMSC were long-lasting (several weeks) and equally efficient whether administered in the early or late stages of nerve injury-induced neuropathic pain [109].

BMMC also exhibit an antiallodynic and antihyperalgesic profile, as shown in different models of neuropathic pain. The first study suggesting an effect on pain was published by Klass et al. [110] in rats undergoing CCI. The authors found that intravenous injection of BMMC on the same day of injury reversed mechanical allodynia and thermal hyperalgesia in rats with persistent neuropathic pain, 10 days after injury [110]. The effect was not immediate, which suggested that BMMC treatment does not prevent neuropathic pain [110]. This study was followed by another one where the unilateral injection of BMMC in the skeletal muscle of the hindpaw was practised in rats with diabetic neuropathy [111]. In these rats, BMMC treatment resulted in a reduction of mechanical and cold hyperalgesia, and improvements in vascular flow, conduction velocities of sensory and motor nerves in the treated limb [111]. Interestingly, it seems that this effect may be dependent on the age and health of the donor, since the use of BMMC from old or diabetic rats exhibits impaired therapeutic effects [112].

The most recent published study in rats shows that systemic transplantation of BMMC on the same day of sciatic nerve crushing completely prevents mechanical allodynia [113], in contrast to the observations by Klass et al. [110] described above; in fact, BMMC-treated rats remained pain-free throughout the assessed period compared to untreated rats [113]. Furthermore, this effect seems not only to be preventive, as rats treated with BMMC 7 days after induction of sciatic nerve crush also show a more rapid recovery from allodynia, as compared to untreated rats (Brumovsky, Setton-Avruj, unpublished results). The difference between studies, with delayed antiallodynic effect described by Klass et al. [110] vs. the immediate effect observed by Usach et al. [113] when rats are treated with CMMO, remains to be clarified. However, each study addressed chronic (CCI) vs. acute neuropathy (sciatic nerve crush), respectively. It could be speculated that the severity of the injury had an influence on the efficacy and efficiency of effect of CMMO.

Finally, the benefits derived from the use of BMSC and BMMC, and the potential mechanisms involved, have also been recently addressed in the context of several other pain-inducing conditions, including cancer [114].

Influence of BMSC and BMMC on peripheral nerve regeneration

In the first studies addressing the beneficial role of transplanted undifferentiated BMSC in the regeneration of damaged peripheral nerves, Cuevas et al. [23, 115] showed that rats receiving an injection of BMSC in the distal stump of the transected sciatic nerve had significant improvements on the walking track test, along with complete and uniform re-connection between the proximal and distal stumps, as shown from day 33 after injury. Moreover, the authors also showed that the effect was long-lasting (improved locomotion up to 180 days after injury) [23], and depended on the homing (migration) of BMSC at the site of injury [115].

In agreement with the initial studies described above, it was observed in rats with full sciatic nerve transection and a 15 mm gap, that the use of a silicone tube containing BMSC suspended in gelatin and various supporting substances results in improved walking behavior, reduced loss of gastrocnemius muscle weight and electromyography magnitude, and a greater number of regenerating axons and elevated neurofilament and MBP protein levels within the tube [116]. Importantly, the authors also showed elevated expression of various neurotrophic factors within the tubes, including NGF, BDNF and GDNF, at both early and late phases of transplantation [116]. Similar outcomes were observed using BMSC-loaded epineural tubes [117], inside-out vein [118] or artery conduits [119] and chitosan conduits [120-121], as well as the combination of BMSC and experimental axonal regeneration promoters such as chondroitinase ABC (see [122-123]).

BMMC have also emerged as an interesting option for the treatment of damaged nerves. Thus, it has been shown that BMMC transplanted directly between the proximal and distal ends of the axotomized sciatic nerve in rats, facilitates myelin formation and axonal regeneration of the injured nerve [97, 124-128]. Furthermore, a reduction in neuronal cell death and enhanced axonal outgrowth in the DRG neurons *in vitro* of rats treated with BMMC was also observed [97]. More recently, the beneficial effect of BMMC on peripheral nerve regeneration has been addressed in rats with sciatic nerve crush, and after intravascular administration of the experimental cells [113, 129]. Here, the pro-regenerative effect began within a week of treatment with intravascular BMMC, with treated rats showing clear signs of axonal recovery and untreated rats maintaining the typical WD alterations, with presence of large numbers of residual myelin and axons. Only by day 21, improvements were also evident in untreated rats, although never reaching the level of improvement observed in BMMC-treated animals [113, 129].

Mechanisms of action of BMSC and BMMC in their role as modulators of neuropathic pain and peripheral nerve regeneration

Migration and implantation

One of the earliest hypotheses to explain the mode of action of BMSC after their administration in animals with peripheral nerve injury suggested that these cells migrate towards damaged tissues. This was shown in rats with single ligature nerve constriction, where BMSC transplanted directly into the L4 dorsal root ganglion (DRG) of the injured rats resulted in prevention of mechanical and thermal allodynia, accompanied by migration and colonization of other ipsilateral (but not the contralateral) ganglia affected by the injury (L3, L5 and L6) [Figure 1], and modification of the expression levels of neuropeptides and other neuromodulators [108, 130-131]. More recently, it has been observed that intrathecal administration of BMSC in rats with CCI or SNI results in migration of these cells towards injured DRGs, as early as 3 days after treatment and with clear, long-term consequences in pain-like behavior [109].

The observation of a migratory behavior for BMSC led to the question of what type of chemoattractants dictate the migration of BMSC towards damaged tissue. Monocyte chemoattractant protein-1α (MCP-1α) and stromal cell-derived factor-1 (SDF-1; derived from the CXCL12 gene) are two chemoattractants shown to participate in the migration of BMSC, both *in vitro* and *in vivo* [132-134]. Interestingly, crushing of the sciatic nerve induces the expression of MCP-1α and SDF-1 in small and medium DRG neurons, and glial cells, respectively (*Coronel, personal communication*), and of SDF-1 in SC present in the distal end of the injured nerve [135]. Moreover, an increase in ganglionar immunoreactivity for MCP-1α has been described after direct compression of a spinal ganglion [136]. Importantly, BMSC express the surface proteins CXCR4 and CCR2, acting as SDF-1 and MCP-1α receptors, respectively [134]. More recently, the BMSC chemoattractant role of SDF-1 was further confirmed in mice with CCI or SNI receiving intrathecal BMSC [109]. In these mice, upregulated levels of SDF-1 were observed in ipsilateral L4-6 DRGs, and *in vitro* analysis showed that SDF-1 induces mouse BMSC migration, whereas the use of a CXCR4 antagonist blocked such behavior [109]. Moreover, intrathecal administration of CXCR4 siRNA-treated BMSC in injured mice showed a progressive compromise of the BMSC-dependent antiallodynic effect, along with a reduction in the number of BMSC present in the ipsilateral L4-6 DRGs [109].

Other chemoattractant molecules potentially involved in BMSC migration and nesting in injured tissues are various adhesion molecules such as transient axonal glycoprotein 1 [137], gicerine [138] and N-cadherin [139], all showing altered ganglionar expression after a peripheral nerve injury. Similarly, expression of adhesion molecules such as NCAM and L1-CAM is regulated by changes in the electrophysiology of neurons during sciatic nerve injury [139]. In summary, tissue injury appears to create a microenvironment that allows the recruitment and implantation of circulating BMSC in the injured ganglia, and possibly also nerves (see below).

In contrast to BMSC, migration and implantation of BMMC has been addressed so far in the context of the damaged nerves. In particular, it has been reported that cells lacking typical SC morphology and expressing the multipotent markers CD34, CD90 and CD105 are present in the crush site and distal end of the injured nerves within the first 5 days after injury, which suggests the arrival of endogenous [129] or transplanted BMMC [113, 129]. These findings also reinforce the concept of an endogenous repair mechanism consisting of BMMC recruitment triggered by peripheral nerve injury. However, the mechanisms involved remain to be established, as well as whether BMMC also migrate and nest in DRGs or spinal cord areas affected by peripheral nerve injury.

Transdifferentiation

Once implanted in mouse DRGs, BMSC have been shown to survive for prolonged periods of time (only showing a sharp decrease 70 days after administration) [109]. Such a long survival entertained the idea of transdifferentiation within DRGs, especially after reports showing that transplanted BMSC in the CNS begin to express neuronal and astrocytic markers [57, 89]. However, in rats with single ligature nerve constriction and intraganglionar administration of BMSC, no signs of transdifferentiation were found, as shown by the lack of expression of neural or glial markers in the implanted cells (*Coronel, personal communication*). More recently, presence of many CD90-positives BMSC has been shown 28 days after intrathecal administration. However, no signs of trans differentiation into neurons, glia or monocyites was obtained [109]. While more research is needed to completely rule out processes of BMSC transdifferentiation within DRGs, it seems that, at least in mice with peripheral neuropathy, the positive effects on pain behavior did not depend on the differentiation of BMSC but on their interaction with neurons and possibly also glial cells (see below).

In contrast, the pro-regenerative role of BMSC on damaged axons of animals with peripheral nerve injury appears to depend, at least in part on transdifferentiation. Studies in vitro have shown that BMSC differentiate into cells with morphology and phenotype characteristic of SC, as shown by their expression of neurotrophin factor p75 (p75NTR), S100, O4 and GFAP [115, 140-141]. Tohill and Terenghi [49] observed that treatment of bone marrow MSC with the SC mitogen glial growth factor induces the synthesis of GFAP and S100β, and results in the identification of a small population of SC-like cells among cells treated as such. In support, *in vivo* studies in rat by Dezawa et al. [22] and Mimura et al. [24] showed that these BMSC-derived SC transplanted into artificial grafts used to reconnect completely severed sciatic nerves maintain their SC phenotype (as shown by their expression of mature SC markers) [24], promote myelination and neural regeneration, and facilitate the reconnection between the proximal and distal ends of the injured nerve within the first 6 months after injury [24]. Importantly, animals receiving such

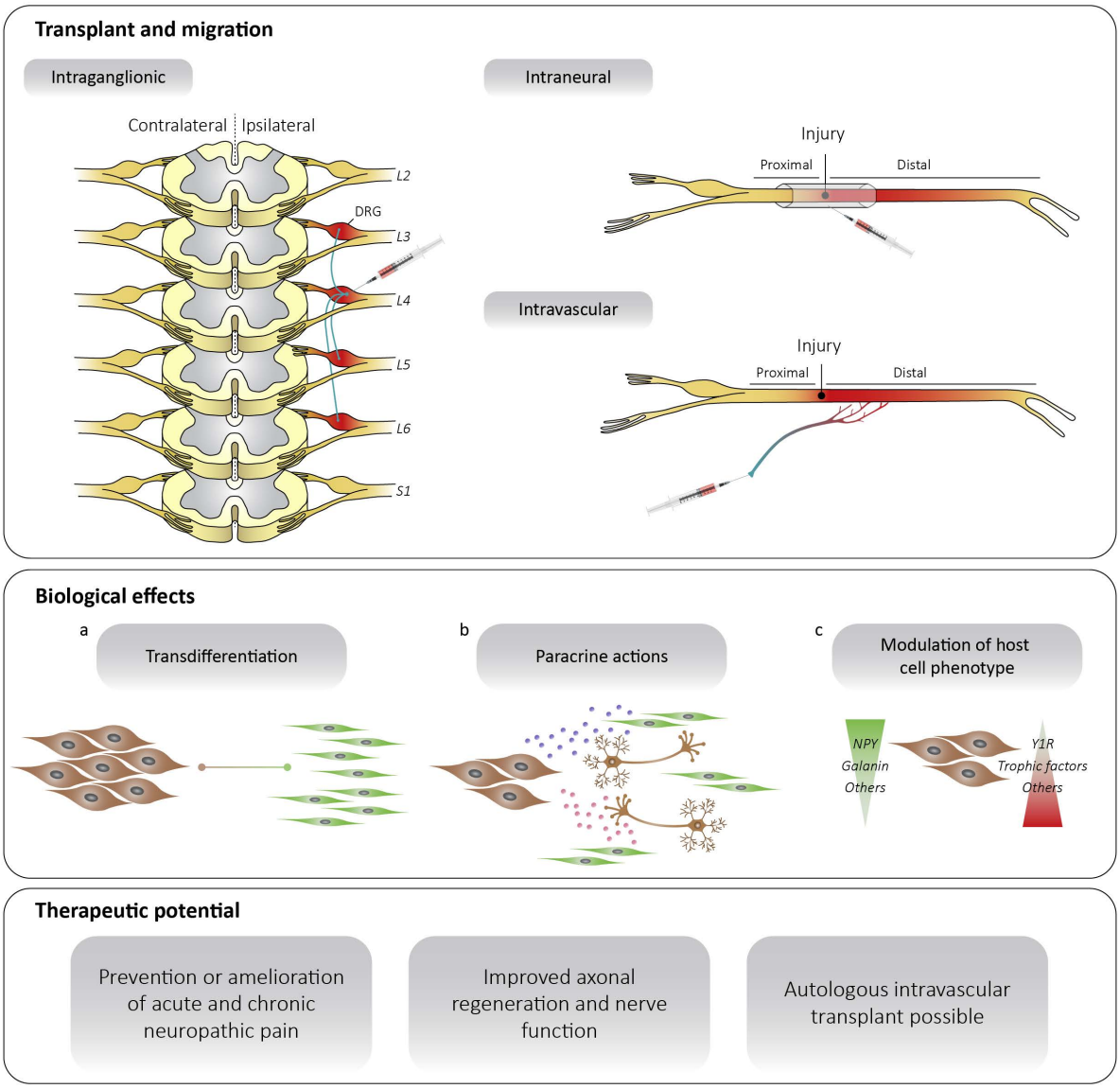

Figure 1: Possible therapeutic implications of BMSC and BMMC transplant for the treatment of peripheral nerve injury. The results presented in this review demonstrate that the intraganglionic, intraneural or intravascular transplant of BMSC or BMMC results in their migration and specific recruitment by injured areas, partly due to chemotactic factor secretion. The migration and nesting of BMSC and BMMC after injury results in various proposed biological effects: a) transdifferentiation to Schwann cells or neurons, b) paracrine actions with the release of neurotrophic factors, among others, and c) the modulation of host cell chemical phenotype, altering protein expression in DRGs, nerves and the spinal cord. Bone marrow cell therapeutic potential is high, with effects on neuropathic pain, axonal regeneration and nerve function as the most prominent. All this evidence suggests that transplantation of BMSC and BMMC, especially through the systemic route, could be considered an attractive therapeutic strategy in the treatment of patients with acute or chronic pain.

transplant showed a significant improvement in motor behavior and in nerve electrophysiological properties, as compared to control groups [24]. Finally, intraneural administration of undifferentiated BMSC in the distal stump of the axotomized rat sciatic nerve results in their migration and integration [23], as well as in the acceleration of motor recovery [23, 115-116, 142]. Moreover, such physiological effects may also be dependent on transdifferentiation, as suggested by the observation that even undifferentiated BMSC transplanted into an artificial conduit to repair severed sciatic nerves in the rat are found to express S100β [48, 142].

BMMC also appear to undergo transdifferentiation after nesting in injured peripheral nerves. BMMC contain an enriched population of lymphocytes, monocytes, hematopoietic progenitor cells, endothelial progenitor cells and BMSC. Prior transplantation, BMMC phenotype analysis shows a small proportion of CD34+ and CD105+ cells as well as a high proportion of CD90+ cells compatible with the presence of multipotent cells [113, 143]. However, once nested, some of these cells, labelled using the fluorophore 5-(and 6)-((((4-chloromethyl) benzoyl) amino) tetramethylrhodamine (CMTMR), are observed to express SC markers S100β and MBP, both distally and in the injured area [129]. Moreover, further studies using the transgenic strain Wistar-TgN(CAG-GFP)184ys have shown morphological changes in transplanted cells from round-shaped to spindle-shaped, together with the expression of SC markers [143]. Finally, some cells also express the neural marker PGP 9.5 and exhibit small size, round shape and two nuclei [129].

Paracrine actions

Regardless of their phenotypic fate (transdifferentiation vs non-transdifferentiation), it is becoming clear that implanted BMSC or BMMC exert their effects by means of paracrine actions. In agreement, neuroimmunomodulation has recently been proposed as a relevant mechanism to explain the pro-regenerative role of BMSC [113, 144-145]. With such hypothesis in mind, nested BMSC and BMMC could functionally be thought as glia-like cells, synthesizing and releasing trophic factors to promote the survival of damaged sensory neurons and axons. In fact, BMSC constitutively secrete a broad spectrum of cytokines, growth factors and chemokines, and express chemokine receptors [116-117, 122-123, 134, 146-148] that, in their natural environment, the bone marrow, modulate the survival, proliferation and differentiation of HSC and their progeny [146, 149]. In support, an increase in the production of nerve and brain-derived nerve growth factors (NGF and BDNF, respectively), with parallel functional recovery, has been demonstrated following the administration of BMSC to animals with brain injury [87] or spinal cord trauma [84]. Accordingly, NGF, BDNF and vascular endothelial growth factor (VEGF) expressions have been detected in transplanted BMSC in rats with sciatic nerve axotomy [117, 122-123], which appears to contribute to the higher content of such and other growth factors in the regenerated tissue [116].

NGF [150-151] acts through the activation of the low affinity receptor $p75^{NTR}$ [152], and the high affinity receptor TrkA [153], both expressed in primary afferent neurons [154]. Interestingly, an increase has been observed in the levels of the active phosphorylated form of the TrkA receptor in the DRGs of animals with single ligature nerve constriction and intraganglionic injection of BMSC (*Coronel, personal communication*), suggesting a greater activity of the NGF signaling pathway. It remains to be established whether the potentially higher NGF activity is due to secretion from BMSC, or from satellite ganglion cells within DRGs.

The quick onset of antinociceptive actions of BMSC nested within the lumbar spinal cord [107, 109], lumbar DRGs [109, 130] and the prefrontal cortex [107] after systemic [107], intraganglionic [109, 130] or intrathecal [109] administration further supports the hypothesis of paracrine actions [107-109, 130]. In fact, after their intrathecal administration and homing in the spinal cord and DRGs, BMSC synthesize and secrete large amounts of transforming growth factor beta 1 (TGF-β1), an anti-inflammatory cytokine *per* excellence. Such BMSC-dependent secretion of TGF-β1 appears to modulate pain-like behavior in rats with CCI, since its blockade using antibodies or small interfering RNA resulted in neutralization of the antiallodynic and antihyperalgesic effects of intrathecal BMSCs [109]. Furthermore, the exogenous administration of TGF-β1 in rats with CCI potently inhibited neuropathic pain [109]. In contrast, the release of the anti-inflammatory interleukin 10 (IL-10) from BMSCs was very low, and did not seem to contribute to the BMSC-induced pain relief, as shown by the lack of effect of IL-10 neutralization on the pain relief induced by intrathecal BMSCs [109]. All these observations are in agreement with a number of known actions for TGF-β1, including: 1) a reduction in the activation and proliferation of spinal and ganglionar microglia, 2) the suppression of the excitatory synaptic transmission in neurons of the outer lamina II of the spinal cord, and 3) a reduction in the frequency of neuronal action potentials of the DRGs (see [109]). Finally, the anti-inflammatory actions exposed thus far for BMSCs appear to also include the change from a pro-inflammatory to an anti-inflammatory state of macrophages and a reduction in the presence of pro-inflammatory interleukins (IL), as well as the induction of synthesis and secretion of the anti-inflammatory cytokine IL-10 [107, 155]. Moreover, it has even been suggested that the effect of BMSC on neuropathic pain involves the endogenous peripheral and central opioid system [106].

Similar paracrine actions could also be attributed to BMMC, although this remains to be established. Interestingly, it has been suggested that the heterogeneity of cellular types included in the mononuclear fraction of the bone marrow could offer additional advantages, as synergistic interactions between the different cell types could potentiate paracrine actions and their pro-regenerative and antinociceptive actions [93]. Mechanistically, the non-stromal population may be thought as a source of cytokines and growth factors, contributing to the enhancement of survival and proliferation of the stromal fraction [156]. In support, increased expression of BDNF and glial derived neurotrophic factor has been shown in the injured sciatic nerves of rats treated with BMMC [127]. Likewise, BMMC treatment in rats undergoing diabetic neuropathy showed increased levels of VEGF, fibroblast growth factor and insulin-like growth factor in the treated nerves [157]. Such higher expression of trophic factors seems to be functional, as suggested in a study in rats with complete nerve transection, where co-administration of neutralizing antibodies for NGF (but not BDNF) with BMMC resulted in reduced neurite growth of sensory and sympathetic neurons maintained in vitro [97].

Modulation of host cell phenotype

BMSC and BMMC modulation of pain and nerve regeneration after their migration, nesting, and chemical interaction within the injured tissue has been described in detail in the sections above. However, what type of influence do these cells have on the target tissue that alters the evolution of pain and regeneration?

One answer to this broad question appears to be changes in the neurochemical phenotype of local neurons/cells in the vicinity of the implanted cells. This is supported by a study where intraganglionic BMSC were shown to partially prevent the upregulation of the expression of the neuropeptide tyrosine (NPY) and galanin (GAL) in DRG neurons in rats with peripheral nerve injury [130]. Likewise, intraganglionic BMSC prevented the decrease in the number of NPY Y1R-positive neurons [130]. It is known that NPY and GAL are actively involved in the modulation of nociception, with anti- and pronociceptive actions being attributed to both peptides [158-165]. Such disparity in their actions is related to the ability of these peptides to bind to different subtypes of associated receptors [166-167]. As for NPY, there is evidence to suggest that Y1R is predominantly antinociceptive [164-165, 168-169], whereas Y2R would mediate NPY proalgesic actions [163-164]. Conserved levels of Y1R in primary afferent neurons in rats treated with BMSC presuppose the maintenance of its transport to the primary afferent terminals of the spinal cord, where its activation has been shown to reduce intraspinal secretion of excitatory neuropeptides such as substance P [170-171]. In addition, maintained Y1R expression at the cell body level, plus some degree of NPY expression in DRG neurons of rats with peripheral nerve injury treated with BMSC could facilitate the occurrence of a phenomenon of intraganglionar "cross-signaling" among different neuronal populations, facilitating the NPY-dependent inhibition of Y1R-positive nociceptors. Altogether, the persistence of Y1R at the ganglion and spinal levels in rats with peripheral neuropathy treated with BMSC could be one mechanism participating in the alleviation of pain.

The analysis described for the NPYergic system cannot be done in relation to GAL, since there is a lack of reliable antibodies for the detection of its receptor GalR1, clearly associated with the inhibitory effects of the peptide [159]. However, as with Y1R, sciatic nerve injury has been shown to induce a decrease in mRNA expression of both GalR1 and GalR2 in primary afferent neurons [172-174]. If BMSC had the same preventive effect on GalR1 as observed with Y1R, then the persistence of GAL expression in the injured ganglia of BMSC treated rats could also participate in intraganglionar "cross-signaling" and spinal inhibition of pain.

Finally, it has also been shown that combined BMSC transplantation and chondroitinase ABC therapy in a model of acellular nerve allograft repair of the sciatic nerve in rats results in increased expression of NGF, BDNF and VEGF in the regenerated nerve [123]. Interestingly, it has also been shown that expression of these factors is also upregulated, and positively influences growth, in distal tissues such as target muscles and the spinal cord [123]. As mentioned in the previous section, it is very likely that these and other factors had BMSC and BMMC as sources [116-117, 122-123, 134, 146-148]. However, an additional possibility is that BMSC and BMMC promoted the synthesis and release of different trophic factors by local injured and distant associated tissues.

Modulation of the nerve degeneration-regeneration process

After sciatic nerve crush, neutrophils initiate infiltration of the distal area (within 8 h after injury), although their presence is short-lived [175]. Over the first days, monocytes are recruited to complete the degeneration process [176]. Considering the BMMC composition [113] and their regenerating ability after WD, the small amount of remaining transplanted granulocytes may be speculated to leave the injured area within the first hours, together with endogenous ones, which might confirm the key role of the mononuclear fraction in the beneficial effects observed on sciatic nerve regeneration.

Therefore, BMMC may collaborate in the removal of myelin debris generated by a neuropathic lesion during demyelination, as an essential step to foster remyelination [113, 127, 129]. Importantly, the faster recovery of myelin sheath and damaged nerves in these animals translates into significant improvement in motor behavior and in nerve electrophysiological properties [24, 113, 129].

Translational implications

The lack of effective and well-tolerated therapies for the treatment of neuropathic pain [30-31, 177], and the almost complete lack of effective methods to allow satisfactory regeneration of damaged peripheral nerves, stresses the need for the development of new therapeutic options. As described throughout this review, the concept of cell therapy using stem cells has gained considerable momentum, attracting the attention of the international scientific and medical community [178-180].

Thinking with a translational perspective, BMSC and BMMC transplantation emerges as an interesting strategy. When focusing on BMSC, these are easy cells to isolate from the bone marrow and to purify, because of their typical adherence to plastic and the propensity to expand in culture [59]. Moreover, the use of BMSC avoids ethical and immunological concerns otherwise associated with the use of mesenchymal cells of embryonic origin. Finally, BMSC produce a large variety of cytokines and growth factors, either *in vitro* or *in vivo* [87, 147-148], which promote mechanisms of endogenous repair of injured tissues [87], further contributing to functional recovery [89].

Intraganglionic administration of BMSC in the preclinical setting has been considerably useful to expose some of the potential mechanisms behind the antinociceptive effects of this type of cells in rodent models of chronic pain [108, 130-131]. However, one important limitation of this experimental model is its route of administration; intraganglionic injection is technically complex, and could hardly be used in patients. Alternatively, the use of the intrathecal space for the administration of BMSC appears as a perfectly valid approach, especially in patients refractory to pharmacological treatment and already implanted with an intrathecal catheter [109]. Systemic transplantation of BMSC would certainly be a step forward in the search of a therapy less invasive for the treatment of chronic pain and the improvement of nerve regeneration, and several preclinical examples have been included in the present review (see previous sections). Importantly, BMSC are currently being addressed in the clinical setting, in trials assessing their effects in patients with lumbar disc degeneration [181] or knee osteoarthritis [182], after intradiscal or intraarticular administration, respectively. The results are promising, showing significant improvements in pain and disability assessments, and with favorable rates of safety and therapeutic feasibility [181-182].

Despite the clear potential of BMSC as useful therapeutic agents, one of the most important limitations for their use is the *ex vivo* cellular manipulation required to obtain them [74]. Therapies based on the use of BMSC would require sampling through bone marrow puncture of the patient, isolation of BMSC and its expansion in culture. These procedures are expensive, laborious and do not always generate the optimum amount of cells. Moreover, phenotypical rearrangements have been reported in cultured BMSC [92]. Likewise, considering that many injuries that require regenerative techniques are the product of emergent situations such as car accidents, time becomes a determinant factor for which techniques depending on cell culture end up being ineffective. With such perspective, BMMC appear as an interesting alternative [113] and may be favored by three important aspects: 1) the immediate availability of cells for acute intervention, which would minimize potential malignant transformations [183] and phenotypic rearrangements [92] that exhibit BMSC throughout their culture passages, and would eventually allow autologous transplantation (only 60 minutes would be necessary for bone marrow isolation, obtaining BMMC and intravascular injection) [121, 184]; 2) intravascular BMMC transplantation is a minimally invasive procedure [185]; and 3) the spontaneous migration of the transplanted cells collaborates with the morphological and functional recovery. These three factors suggest that such an approach has the potential to avoid associated costs [184], and problems such as contamination and the need for infrastructure conditions for Good Manufacturing Practices [186].

In previous sections, we have also presented several preclinical examples supporting the value of systemic BMMC transplantation as anti-allodynic and pro-regenerative agents, and comparable to those seen with systemic or intrathecal BMSC administration. Accordingly, BMMC transplantation is being addressed in clinical trials in patients with acute myocardial infarction (intramyocardial and intracoronary transplantation) [187-188] and with traumatic brain injury (intravenous transplant) [189], showing that BMMC treatment is feasible, safe, and results in improved cardiac function [187-188], as well as structural preservation of critical SNC architecture with downregulation of inflammatory biomarkers [189]. In addition, autologous BMMC injection in ischemic stroke patients has shed light on optimal cell doses, especially after intraarterial transplant [190].

In these cases, cellular therapy is well-tolerated and opens new perspectives in the treatment of peripheral arterial diseases [190-191]. Moreover, clinical trials using intraspinal injection of autologous BMMC has proven to be feasible and safe in patients with amyotrophic lateral sclerosis, even if further assays are necessary to reach conclusive results [192]. While these studies show promise, more preclinical and clinical research will be required to establish the degree of benefit obtained from BMMC transplantation, for the treatment of neuropathic pain and peripheral nerve injury. The only available study thus far is by Braga-Silva et al. [193], where BMMC-filled silicone tubes used to connect the ends of the median and ulnar nerves in human patients, showed better recovery than empty tubes.

Concluding remarks

Topical or systemic transplantation of BMSC and BMMC in animals with peripheral nerve injury results in their migration and selective nesting in injured neural tissues (compressed nerves, DRGs, spinal cord). This is associated with a sharp reduction in pain manifestations, mitigation of the neurochemical changes usually observed in DRG neurons during peripheral nerve injury, and a faster degeneration-regeneration process, accompanied by improved electromyographic properties (Figure 1). Such beneficial effects are in agreement with similar observations made in various animal models of injury or disease of the nervous system, such as infarction [194], ischemia [86], cerebral trauma [89, 195], Parkinson's disease [196], contusion injury [83, 88, 197] and demyelinating processes of the spinal cord [57]. In these models, the successful migration and implantation in injured areas of intravascularly administered rat mesenchymal stem cells has also been associated to symptomatic recovery and regeneration.

The effect on pain-like behavior of BMSC- and BMMC-treatment in injured animals is direct and immediate, and shows both the capacity to prevent or ameliorate pain. Also, BMMC transplantation reduces the time required to observe the onset of effective recovery of damaged nerves by at least 2 weeks, as compared to untreated rats. This improvement in recovery time is significant, considering that the gestation period of the rat is 21 days, a 70-day old rat is already considered adult, and its average life is 2 years.

Based on the experimental studies described in this review, the hypothetical series of events associated with BMSC and BMMC transplant upon peripheral nerve lesion can be summarized as follows: 1) endogenous or transplanted BMSC or BMMC selectively migrate and nest within injured nerves/ganglia/spinal cord, presumably due to the presence of a chemotactic environment, which may facilitate the arrival of the transplanted cells to altered tissues; 2) BMSC/BMMC exert an early immunomodulatory action through the synthesis and release of trophic factors and anti-inflammatory cytokines such as IL-10 [107] and TGF-β1 [109], among other molecules; 3) this leads to reduced activation and proliferation of microglia and astrocytes, suppressed excitatory synaptic transmission, and a lower frequency of action potential generation [107], among the few described effects thus far; 4) later, BMSC and BMMC transdifferentiate into neuronal and/or glial phenotypes, probably to replace damaged cells in the lesion area and potentially leading to long-term effects [143]; and 5) pain is reduced and nerve regeneration is enhanced as a consequence of all these changes.

Despite the points summarized above, much is still to be learnt about the exact mechanisms by which transplanted BMSC and BMMC modulate the activity of primary afferent neurons and injured nerves and favor immediate recovery from pain and latency-mediated morphological and functional regeneration [108, 113]. In addition, it also remains to be addressed if transplanted BMSC and BMMC could be useful in the treatment of other pain-associated conditions, such as inflammatory pain, visceral pain, and in gene-related pathologies such as Fabry's disease, with neuropathic pain as one salient symptom.

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