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Bone marrow-derived mesenchymal stem cells alleviate paclitaxel-induced mechanical allodynia in rats

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Abstract

Anticancer drug paclitaxel (PTX) frequently causes painful peripheral neuropathy; however, no medication has been shown to be effective in the treatment of this debilitating side effect. We aimed to investigate the efficacy of two different doses of allogeneic bone marrow-derived mesenchymal stem cells (BM-MSCs) on PTX-induced mechanical allodynia and spinal cytokine levels and their localization to target tissues such as the spinal cord and sciatic nerve. After the development of mechanical allodynia with repeated PTX administration, two different doses of rat BM-MSCs, low or high (1×10^6–5×10^6), were transplanted into rats and the evaluation continued for 30 days. Interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-10 levels in spinal cord samples of animals were analyzed by enzyme-linked immunosorbent assay. PTX-induced mechanical allodynia was relieved significantly 15 days after the transplantation of high-dose of BM-MSCs. Both MSCs doses were effective in alleviating allodynia, but the onset of effect was earlier with the high dose. High-dose of BM-MSCs significantly decreased spinal IL-1β and TNF-α levels compared to the PTX group. Fluorescent dye-labeled BM-MSCs were observed much more frequently in the sciatic nerve and spinal cord samples of the high-dose BM-MSCs transplanted group than in the low-dose group animals. In conclusion, we found that the antiallodynic effects of BM-MSCs appeared earlier when high-dose of cells were administered. We think that other mechanisms may play a role in the effects of MSCs, besides localization to damaged tissues and reducing spinal inflammatory cytokine levels. We show that BM-MSCs can be a novel approach in PTX-induced mechanical allodynia.

KEYWORDS
mechanical allodynia, mesenchymal stem cells, neuropathic pain, paclitaxel, rat

1 | INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious, dose-dependent adverse effect of several anticancer drugs. Paclitaxel (PTX) is a widely-used anticancer agent for the treatment of several types of cancers. PTX causes dose-dependent CIPN and neuropathic pain, which can lead to dose reduction or treatment cessation, with affects the quality of life of cancer patients.[1] The clinical management of these patients became a problem as current pain medications are ineffective and display many side effects. Various attempts have

been made; however, no medication has been shown to be effective in the treatment and prevention of CIPN.[1,2] Mitochondrial dysfunction related to oxidative stress has been identified as one of the primary mechanisms of CIPN.[3] Additionally, the chemotherapy-induced injury-activated inflammatory process has been considered a potential trigger of nociception.[4]

Mesenchymal stem cells (MSCs) have been indicated as a novel emerging regenerative therapy due to their ability to self-renew, multipotency, and secretion of various paracrine neurotrophic factors and cytokines, exerting neurosupportive effects.[5] Studies have revealed the therapeutic potential of MSCs for some chronic pain conditions.[5–8] Most of the studies related to the effectiveness of MSCs in pain conditions have focused on diabetic neuropathy or nerve injury models.[9,10] It was shown that systemic applications of MSCs reduced mechanical allodynia and thermal hyperalgesia in rodent chronic constriction injury,[9] spinal cord injury,[10] and diabetic neuropathy models.[11] Intrathecal injection of MSCs has also been reported to reduce mechanical allodynia and thermal hyperalgesia in a rat spinal cord injury model.[5] Recently, a few studies have shown the effectiveness of MSCs in the platinum drugs[6,7] and PTX[7,8] induced neuropathy in rodents, so, we aimed to investigate the efficacy of two different doses of bone marrow-derived MSCs (BM-MSCs) in PTX-induced mechanical allodynia, their effects on spinal cytokine levels, as well as homings to the target tissues such as sciatic nerve and spinal cord.

2 | MATERIALS AND METHODS

2.1 | Animals

Forty-two male Sprague–Dawley rats (weighing 180–200 g, 6–8 weeks of age) were obtained from Erciyes University Laboratory Animal Care Facility. The ambient temperature of the room was maintained at 22 ± 1°C, and the humidity was 50%–60% with a light–dark cycle of 12 h. Rats were supplied with standard laboratory rat chow and water ad libitum. Two rats were used for BM isolation. Remaining forty rats were randomly divided into five groups: control, vehicle of PTX; cremophor-EL (Cre-EL), PTX, PTX + BM-MSC 1 million and PTX + BM-MSC 5 million groups ($n = 8$ per group). Due to its low solubility in water, PTX is formulated in a Cre-EL/ethanol (1:1 vol/vol) mixture and diluted in saline before administration to cancer patients. Therefore, the Cre-EL/ethanol content in the vehicle group (Cre-EL) was adjusted to be the same as in the PTX group.

All testings were conducted between 09:00 and 12:00 h. The rats were allowed to adapt to the new environment for at least 1 h before all testing days. Experiments were approved by the Local Ethics Committee for Animal Experiments of our university (no: 15/84) and performed in accordance with relevant ethical guidelines.

2.2 | Isolation and characterization of rat BM-MSCs

Experiments were performed according to the described protocol[12] with minor modifications. Rats were killed by cervical dislocation under ketamine–xylazin anesthesia. Tibias and femurs were dissected immediately and BMs were extruded by Dulbecco's modified Eagle's medium (DMEM; Gibco). The homogenous cell suspension obtained after the filtration and washing steps was resuspended in complete culture media containing DMEM supplemented with 10% fetal bovine serum (Gibco BRL), 1% penicillin/streptomycin (Gibco Invitrogen), and 1% glutamax (Gibco Invitrogen). The cells were seeded in plastic tissue culture flasks and incubated at 37°C, in a humidified 95% air, 5% CO_2 atmosphere. The culture medium was changed when necessary until the cells reached confluency and passaged using 0.25% trypsin-ethylenediamine tetraacetic acid solution (Gibco Invitrogen). Characterization of cells and expression of cell surface markers were determined by flow cytometric analysis, and adipogenic and osteogenic differentiations were determined by histochemical staining.

2.3 | Immunophenotyping and in vitro differentiation of BM-MSCs

Briefly, cell samples (2×10^5 cells/200 μl) were stained for 30 min with specific antibodies against the rat antigens (anti-CD90-FITC [2:1000]; Biolegend, anti-CD45-PE [2.5:1000]; Biolegend, anti-CD79b-FITC [5:1000]; Abcam, anti-CD73 [2.5:1000]; BD Biosciences; and anti-CD105 [8:1000]; Abcam) at room temperature in the dark. Unconjugated antibodies were conjugated with a secondary antibody (Goat Anti-Rabbit IgG H&L Alexa Flour 488 [4:1000]; Abcam). Flow cytometry was performed by using FACS Aria III (BD Biosciences) and data were analyzed with Cell Quest software (BD Biosciences).

Multilineage differentiation of isolated BM-MSCs to adipocytes and osteocytes was tested using the Rat MSC Functional Identification Kit (R&D Systems; SC020) according to the manufacturer's instructions. Briefly, MSCs in a 24-well plate were treated with adipogenic or osteogenic differentiation mediums for 14 days. Cells were fixed with 10% formaldehyde and incubated with fresh Oil red O or 2% Alizarin red S solutions to stain lipid droplets or calcium-rich deposits, respectively, then photographed by an inverted microscope (Leica DMi1).

2.4 | PTX administration and rat BM-MSCs transplantations

The sterile injectable PTX solution (Ebetaxel®; 6 mg/ml in Cre-EL/ethanol 1:1) used in the clinic was obtained from Sandoz Pharmaceutical Company. PTX (4 mg/kg) or vehicle Cre-EL

(Sigma-Aldrich)/dehydrated ethanol 1:1 (Merck) was diluted with saline to create a 4 mg/ml concentration before the intraperitoneal administrations in volumes of 1 ml/kg, on 4 alternate days (D1, 3, 5, and 7; a cumulative dose of 16 mg/kg over 1 week). The dose of PTX was chosen based on a previous study[13] and our preliminary results (data not shown). The control group received an equal volume (1 ml/kg) of saline.

Forty-eight hours after the last dose of PTX (Day 9), 1×10^6 or 5×10^6 rat BM-MSCs in PBS were transplanted through the tail veins of rats. Control and vehicle groups received the same amount of PBS in the same way.

2.5 | Von Frey test

Mechanical allodynia was assessed by measuring the hind paw withdrawal threshold (PWT) force of rats with an electronic Von Frey apparatus (Ugo Basile). This electronic device uses a single unbending filament that applies increasing force (from 0 to 150 g) to the plantar surface of the hind paw over a 20-s period until a paw withdrawal response is elicited. The force at which this response occurs is recorded automatically by the apparatus and is designated as the PWT (g). On each day of the experiment, the animals were acclimated for 1 h in individual transparent perspex boxes (15 cm × 16 cm × 21 cm) with a wire mesh bottom. The basal response to the filament was tested in each animal 3 days before the PTX administration (pretreatment value; D0). PTX or vehicle treatments were performed on Days 1, 3, 5, and 7 and PWT measurements were performed on Days 0, 1, 5, 8, 15, 23, 30, and 38. Mechanical allodynia was determined by a significant decrease in the mean of triplicated PWT measurements from each rat.

2.6 | Labeling cells with PKH26

Before transplantation, some of the cells were labeled with red fluorescent membrane-intercalating dye PKH26 (Sigma-Aldrich) according to the manufacturer's instructions to visualize the migration of cells in the tissues. The staining efficiency was confirmed by fluorescence microscope (Olympus BX51) and flow cytometry and the viability was counted with trypan blue dye under an inverted microscope.

2.7 | Ex vivo analysis

In each group, half of the animals were killed 15 days after (Day 24) BM-MSCs transplantations and the remainings were 30 days after (Day 39) under ketamine–xylazine anesthesia, and spinal cord and sciatic nerves were obtained immediately. Spinal cords were dissected and after weighing the L4–L6 sections were snap-frozen in liquid nitrogen and kept at −80°C until the enzyme-linked immunosorbent assay (ELISA) analysis. Remaining lumbar parts of the spinal cord and sciatic nerves were fixed in 4% paraformaldehyde overnight before being cryoprotected in 30% sucrose for to investigate the homing of labeled cells under fluorescent microscope.

Sciatic nerves and spinal cords were embedded in cryomatrix and sectioned at 7 µm thickness to analyze PKH26 expressions under a fluorescence microscope.

For 1 mg of L4–L6 spinal cord sample 6 µl ice-cold buffer containing 150 mM NaCl (Sigma-Aldrich), 1% Triton X-100, 50 mM Tris pH: 8, and protease inhibitor (Sigma-Aldrich) was used to homogenize by homogenizer (Miccra D-1). Following centrifugation (5000*g* at +4°C for 10 min), the tissue supernatants were collected. After measuring the protein concentrations of tissue supernatants using a BCA Protein Assay Kit (Thermo Fisher Scientific), the commercially available ELISA kits were used for assessing tumor necrosis factor (TNF)-α (ER1393; FineTest), interleukin (IL)-1β (ER1094; FineTest), and IL-10 (ER0033; FineTest) levels according to the manufacturer's instructions. Absorbance was detected at 450 nm with the microplate reader (Multiskan FC; Thermo Fisher Scientific) and the results are expressed as picograms of per milligram of total protein (pg/mg) in the supernatant.

2.8 | Statistical analysis

The results are presented as mean ± SEM and SPSS 21.0 software (SPSS Inc.) was used for statistical analysis. Normality and homogeneity of variances were performed by the Shapiro–Wilk and Levene's tests, respectively. PWT data and cytokine levels between multiple groups were analyzed by one-way analysis of variance and followed by the post hoc Bonferroni and Tukey honestly significant difference tests, respectively. Independent samples *t*-test was performed to compare the cytokine levels between Day 24 and Day 39 in the same group. Differences were considered to be significant at $p < 0.05$.

3 | RESULTS

3.1 | Characterization and labeling of BM-MSCs

MSCs in culture were characterized by their adhesiveness to plastic and spindle-like shape (Figure 1A). In addition, MSCs should express CD105, CD73, CD90, and lack expression of CD45, CD34, CD14, CD79, and HLA-DR surface molecules. Flow cytometric analysis showed expression of CD73 (92.6%), CD90 (99.8%), and CD105 (96.3%), but the lack of hematopoietic markers CD45 (0.3%) and CD79b (2.3%) in isolated MSCs (Figure 1D–H). MSCs also should be able to differentiate between into osteoblasts and adipocytes in vitro. In our study, BM-MSCs were differentiated into adipogenic and osteogenic cell lineages as observed with positively stained specific cell types (Figure 1B,C).

Strong red fluorescence was detected by fluorescence microscopy (Figure 2A) and FACS analysis showed that 91.7% of BM-MSCs

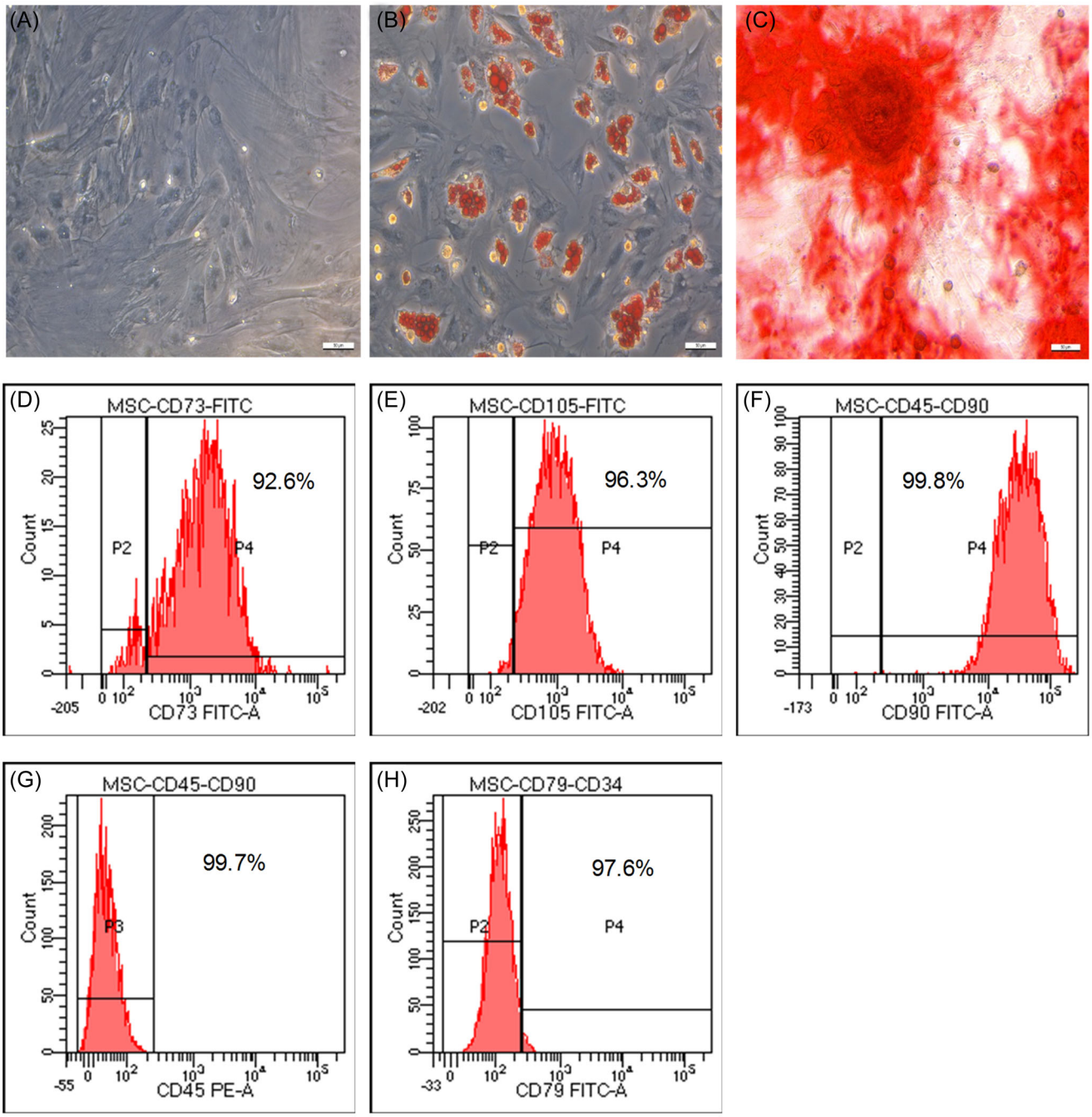

FIGURE 1 In vitro morphology, osteogenic and adipogenic differentiation, and immunophenotypic characterization of BM-MSCs (Passage 3). (A) The morphology of BM-MSCs, (B) adipogenic, and (C) osteogenic differentiation of BM-MSCs (scale bar = 50 μM). Cells were indicated positive for CD73 (D), CD105 (E), and CD90 (F), and negative for CD45 (G), or CD79b (H). BM-MSC, bone marrow-derived mesenchymal stem cell.

were PKH26-positive (Figure 2B). Viability was counted as 93% by trypan blue exclusion (data not shown).

3.2 | PTX-induced mechanical allodynia

Results showed no significant difference in predose PWTs among the groups ($p > 0.05$). PWT was reduced by repeated administrations of PTX and significantly lower than the control group on Day 5 ($p < 0.05$). Cre-EL administration did not significantly change PWT compared to control group ($p > 0.05$). High-dose BM-MSCs, but not low-dose, significantly reversed PTX-induced mechanical allodynia 15 days (Day 23) after the transplantation (PTX-MSC 5 million; 40.4 ± 1.8 g) compared to the PTX group (17.6 ± 1.7 g), ($p < 0.05$). Both doses of BM-MSCs significantly reversed PTX-induced mechanical allodynia at 22

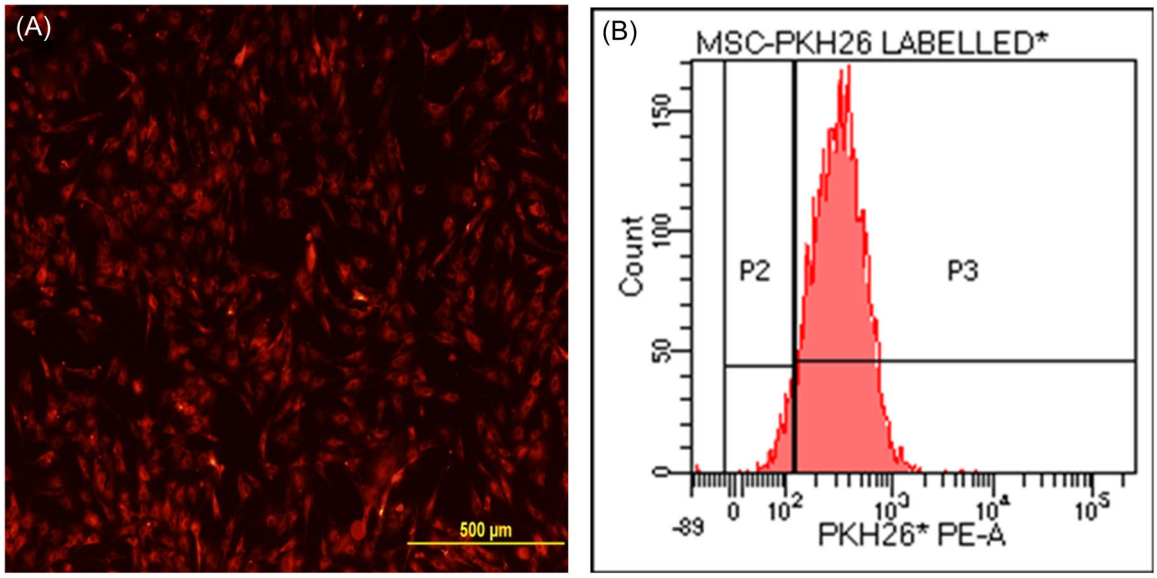

FIGURE 2 BM-MSCs after labeling with PKH26: (A) Strong red fluorescence was detected with fluorescence microscopy and (B) flow cytometry analysis showed that 91.7% of cells were successfully labeled with PKH26. BM-MSC, bone marrow-derived mesenchymal stem cell.

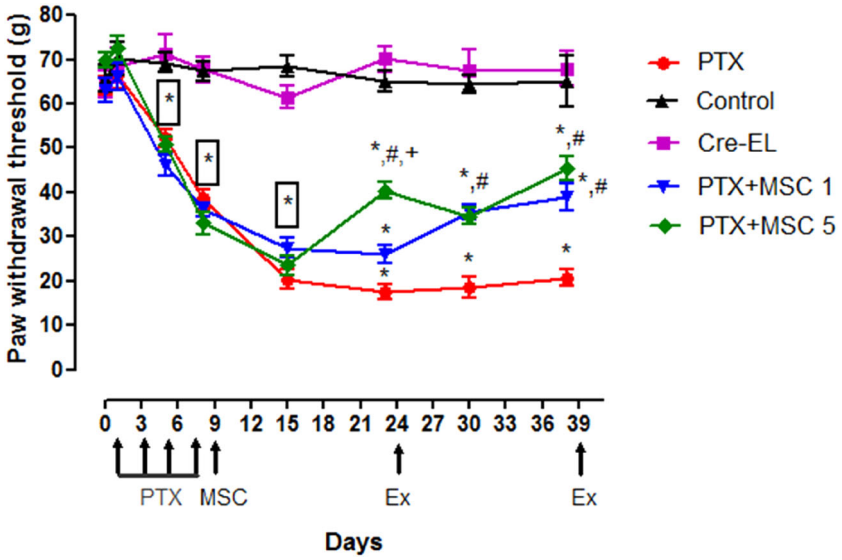

FIGURE 3 Shows that BM-MSCs reverse mechanical allodynia in paclitaxel (PTX)-treated rats in a cell number-dependent manner (MSC 1; BM-MSC 1 million, MSC 5; BM-MSC 5 million). Data are shown as mean ± SEM of eight animals per group until the Day 24, except MSC 5 ($n = 7$). Half of the animals were killed (Ex) at Day 24 and remainings on Day 39. $^{*}p < 0.05$ versus the respective time point of control, $^{\#}p < 0.05$ versus the respective time point of PTX, $^{+}p < 0.05$ versus the respective time point of PTX + MSC 1 million, $^{*}p < 0.05$ when PTX, MSC 1, and MSC 5 versus the respective time point of control group. Statistical analysis was performed using one way-ANOVA followed by Bonferroni's post hoc test. ANOVA, analysis of variance; BM-MSC, bone marrow-derived mesenchymal stem cell; Cre-EL, cremophor-EL.

(Day 30) and 30 (Day 38) days after the transplantation compared to the PTX group ($p < 0.05$) (Figure 3). One animal died 1 day after the transplantation of BM-MSCs in the PTX + MSC 5 million groups. No significant side effects such as ascites, loss of body weight, or any other impairment in animal health were observed with this PTX dosing paradigm, only mild alopecia was observed in the PTX group (data not shown).

3.3 | ELISA analysis

The results showed that administration of PTX significantly increased spinal L4–L6 TNF-α levels compared to the control group on both Days 24 and 39 ($p < 0.05$). Low-dose BM-MSCs transplantation did not induce a significant change in cytokine levels compared to the PTX group; however, high-dose BM-MSCs transplantation

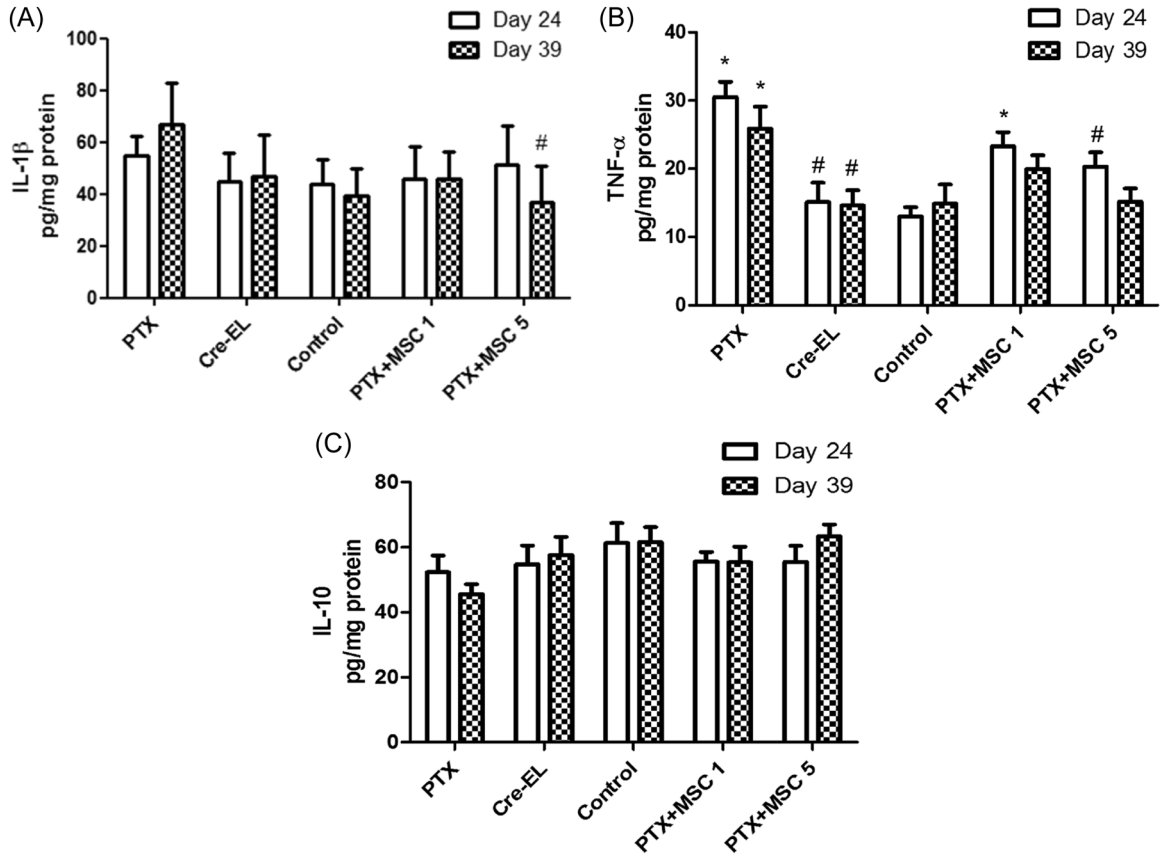

FIGURE 4 Graphs showing the effect of BM-MSCs on paclitaxel (PTX)-induced cytokine production. (A) IL-1β, (B) TNF-α, and (C) IL-10 in the spinal cord (L4–L6) by ELISA. Data are expressed as mean ± SEM. Bars for Day 24 and Day 39 represent sacrification days of rats after the first dose of PTX administration. $^{+}p < 0.05$ versus Day 24 in the same group. $^{*}p < 0.05$ versus control, $^{\#}p < 0.05$ versus PTX in the same day. BM-MSC, bone marrow-derived mesenchymal stem cell; Cre-EL, cremophor-EL; ELISA, enzyme-linked immunosorbent assay; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α.

significantly reduced the levels of TNF-α on Day 24 and IL-1β on Day 39 compared to the PTX group ($p < 0.05$, Figure 4). Change in levels of IL-1β and IL-10 was not significant in the PTX group ($p > 0.05$). Vehicle treatment did not induce a significant change in the cytokine levels of the spinal cord ($p > 0.05$). No significant difference was observed between Days 24 and 39 of the same groups ($p > 0.05$).

3.4 | Homing of cells to the sciatic nerve and spinal cord

We detected red PKH26 labeled BM-MSCs in the sciatic nerve and spinal cord samples. A few PKH26 positive cells were observed in the sciatic nerve and spinal cords of the low-dose BM-MSC transplanted group but were higher in the high-dose BM-MSC group (Figure 5).

4 | DISCUSSION

PTX-induced neuropathy is a significant clinical problem for cancer patients and still, there is no approved treatment for this debilitating condition.[2] The efficacies of MSCs in diabetic neuropathy,[11] peripheral nerve injury,[9] and spinal cord injury[10,14] have been demonstrated in preclinical and clinical studies, but in this study, we showed that MSCs are effective in alleviating PTX-induced mechanical allodynia, possibly by reducing spinal inflammatory cytokine level and homing to damaged tissues.

PTX-induced peripheral sensory neuropathy is associated with dysfunction of mitochondria by the loss of membrane potential in axons.[3,15] In addition to effects on mitochondria and the generation of oxidative stress, chemotherapeutic agents also affect the innate immune system which causes neuroinflammation in the nervous system.[8,15] Chemotherapy-induced injury causes macrophage infiltration, which leads to a subsequent production and secretion of various proinflammatory cytokines, chemokines, and other factors in the DRG.[4] Studies reported that spinal activated astrocytes produce proinflammatory factors including IL-1β, TNF-α, and IL-6 and contribute to the formation of central sensitization and maintenance of PTX-induced mechanical allodynia.[16,17]

Easy isolation and expansion in culture, immunomodulatory effects with low immunogenicity, the ability to migrate to inflammation sites, and differentiation into multiple mesodermal lineages make MSCs an attractive agent in regenerative studies.[18,19] Numerous studies focused on the neuroprotective and neurorestorative

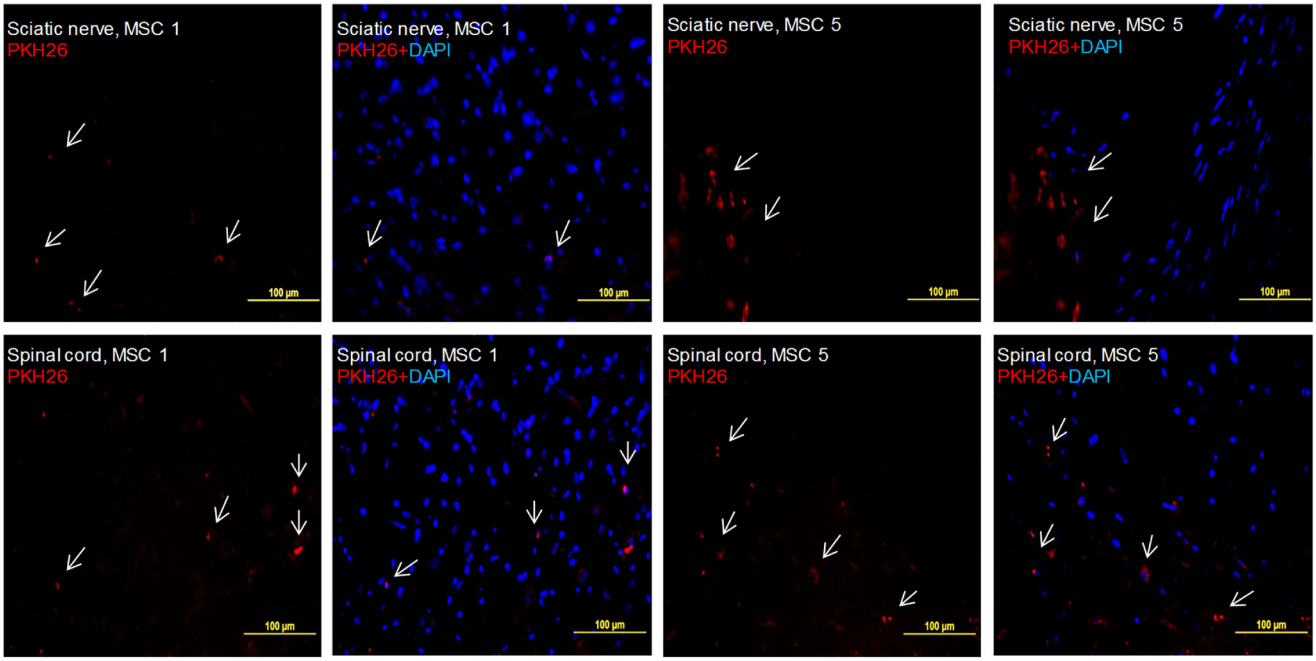

FIGURE 5 Photomicrographs illustrating the homing of intravenous transplanted PKH26 labeled 1 or 5 million BM-MSCs (left) and merged with DAPI (right), in sciatic nerve and spinal cord samples of PTX-treated rats (Day 39). The presence of cells was recognized by red fluorescent signals indicated by white arrows, scale bar = 100 µm. BM-MSC, bone marrow-derived mesenchymal stem cells; DAPI, 4′, 6-diamidino-2-phenylindole; PTX, paclitaxel.

potential of MSCs due to the secretion of cytokines, chemokines, growth factors,[19,20] and also extracellular vesicles to induce regeneration and modulation of the inflammatory response.[21] Our results clearly demonstrate that PTX-induced mechanical allodynia was reduced by BM-MSCs transplantation. Additionally, spinal inflammatory cytokines IL-1β and TNF-α were decreased by 5×10^6 BM-MSCs. In accordance with our results, it was shown that delivery of MSCs could reduce the spinal cord content of IL-1β and TNF-α in rat models of spinal cord injury.[10] There are limited studies in the literature related to the effects of MSCs in CIPNs; in a study by Di Cesare Mannelli et al.[6] intravenous (iv) injection of adipose-derived MSCs (2×10^6) decreased oxaliplatin-induced pain 1 h after the injection which involves the modulation of vascular endothelial growth factor A. After intranasal administration, MSCs have been shown to rapidly enter the brain of mice and reverse cisplatin- or PTX-induced mechanical allodynia by promoting the production of IL-10.[7] In contrast, the fact that we did not find a significant decrease in spinal IL-10 level with PTX administration and increase with MSC transplantations may be due to differences in samples (because we analyzed lumbar part of the spinal cord rather than the spinal meninges), the animal species used, and the administration routes of MSCs. Al-Massri et al.[8] have shown that 1×10^6 BM-MSCs enhanced the thermal antihyperalgesic effect of the anticonvulsant drug pregabaline. In the present study, we focused on mechanical allodynia instead of thermal hyperalgesia as previous studies reported an absence of altered thermal hyperalgesia following PTX administration.[22,23] We evaluated the effects of BM-MSCs on inflammatory parameters in the spinal cord instead of sciatic nerves. In contrast to Al-Massri et al.,[8] we observed very few cells homing to the spinal cord and sciatic nerves when 1×10^6 BM-MSCs were transplanted. Coadministration of pregabalin with MSCs has been reported to increase the homing of cells to the sciatic nerves.[8] We observed that homing was much greater with high dose-BM-MSCs than low dose. Our results suggest that BM-MSCs may exert their beneficial effects partly by reducing the levels of spinal inflammatory cytokines, IL-1β and TNF-α. Factors such as the source and number of MSCs, the neuropathy induction method, the type and dose of the chemotherapeutic agent, and the animal species may be important in the formation of different results.

It was reported that most of the systemically administered MSCs are collected primarily in the lungs, and a number of escaping cells are observed in other organs such as the liver, spleen, and heart. A small number of cells in the bloodstream migrate to the site of wound or inflammation.[24,25] Therefore, we transplanted two different numbers of cells (1 and 5 million) to observe the mechanical allodynia, spinal cord cytokine levels, and homing to spinal cord and sciatic nerves. Our results showed that both 1 and 5 million BM-MSCs were effective at alleviating PTX-induced mechanical allodynia, although in the 5 million BM-MSC group the effect was evident 15 days after transplantation, but appeared later in the 1 million group. Similarly, the homing of 1 million MSCs were relatively small compared to 5 million group. Current results may suggest the communication of cells due to the migration of iv transplanted BM-MSCs to the sciatic nerve and spinal cord. Systemically injected MSCs preferentially localize to injured areas.[9] The paracrine factors released by MSCs play an essential role in the regenerative properties of stem cells.[18] PTX activated inflammatory cells and astrocytes, as well as factors secreted by these cells,[16] may

mediate the homing of BM-MCSs to sites of injury. Sinilsalco et al. suggested that MSCs could exert their pain-reducing effects through a restorative mechanism involving: (i) a cell activation mechanism of spinal cord homed MSCs, results in switching macrophages from pro- to anti-inflammatory state; (ii) communication with other cell types by the secretion of several molecules.[9] In addition to cytokine/chemokine secretion, MSCs also exhibit strong capacity for mitochondrial transfer and microvesicle secretion in response to injury which results in increased tissue regeneration.[18] From our results, we conclude that the efficacy of BM-MSCs in CIPN may be due to their anti-inflammatory effects and homing to damaged tissues, but the involvement of other mechanisms is evident.

The limitation of our study is that we have not conducted any study to analyze the effect of MSCs on the antitumoral activity of PTX. It was reported that MSCs transplantation is safe and does not cause acute infusion toxicity, organ and system complications, infection, malignancy or death.[26] Research on the interaction between MSC and T cells support the potential use of allogeneic MSCs in regenerative medicine and tolerance of allogeneic MSC by recipients,[27] so we used allogeneic BM-MSCs in our study. However, the therapeutic potential of MSCs in cancer is still controversial; MSCs in the tumor micro-environment can confer tumorigenic or antitumor potential to tumor cells dependig on the some factors such as source, dose or timing of MSC treatment and experimental tumor model. Studies have shown the antitumoral activities of MSCs by releasing antiproliferative agents.[28,29] Transplantation of 10×10^7 BM-MSCs by the iv route has been shown to significantly reduce both the initiation and progression of colon cancer by modulating the immune component of the tumor micro-environment.[30] MSC therapy has been recognized as a promising modality for the treatment of clinical diseases, but more detailed knowledge of the interactions between MSCs and cancer cells will undoubtedly lead to more effective clinical therapy in the future.

Our findings suggest that MSCs may have potential benefits for the treatment of PTX-induced peripheral neuropathy, possibly through multiple mechanisms such as reducing neuroinflammation and localization to damaged tissues; however, further studies are needed to elucidate the underlying mechanisms and to prove their safety and efficacy in clinical settings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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