Peripheral nerve injury (PNI) causes sensory and motor deficits as well as neuropathic pain, which seriously impacts patient quality of life (Jiang et al., 2017). Morphological and molecular changes in the spinal cord and dorsal root ganglia (DRG), such as neuronal cell death, nerve fiber degeneration, and glial activation, are strongly associated with PNI-induced pathological syndromes, such as sensitization and abnormal responses to peripheral stimuli and dysregulation of spinal cord circuitry (Calvo and Bennett, 2012; Duraikannu et al., 2019; Zhang et al., 2021). To date, most therapeutic strategies for functional recovery after PNI target the peripheral nerve directly, while only a few treatments target PNI-induced pathological changes in the spinal cord, such as preventing apoptosis-induced neuronal death and inhibiting glial responses. This in part explains why despite continual improvements in therapeutic strategies of PNI over the last few decades, clinical outcomes after PNI remain unsatisfactory, such as suffering from chronic pain. Therefore, there is an urgent need for new therapeutic strategies. Considering the anatomical location of the cell bodies of the peripheral nerve in the spinal cord and DRG and the functional integration between the peripheral and central nervous system, therapeutic approaches targeting PNI-induced spinal cord lesions may benefit post-PNI outcomes. Recently, an in vivo study of the treatment of PNI-induced spinal cord pathological changes through peripheral administration of neural crest stem cells (NCSCs) (2 × 10^5 in a nerve conduit) achieved favorable outcomes after PNI, such as neuropathic pain relief and locomotor function improvements (Zhang et al., 2021). This preclinical study provides insight into the therapeutic potential of a new approach to PNI by targeting PNI-induced spinal cord lesions through peripheral administration of NCSCs, instead of intrathecal injection or transplantation to the injured dorsal root, which holds the potential to translate into clinical practice in the future.

PNI-induced spinal glial responses and neurodegeneration cause neuropathic pain: Different animal models of peripheral neuropathy have observed the glial responses after PNI in both the dorsal horn and the ventral horn of the spinal cord, where the injured sensory afferents terminate and the cell bodies of injured motor neurons are located (Calvo and Bennett, 2012). An increase in glial cell proliferation was shown in the ipsilateral dorsal horn and the ventral horn following PNI, which is the first step of the activation of microglia and astrocytes (Finnerup et al., 2021). PNI-induced activated microglia and astrocytes displayed various specific characterizations in the spinal cord, such as changes in their morphology and gene expression profile, thus participating in the initiation and maintenance of pain (Finnerup et al., 2021). Activated microglia leads to functional changes including recruitment in the injured area, phagocytosis, and production of a variety of pain-associated substances, such as pro-inflammatory cytokines, nitric oxide, prostaglandins, and excitatory amino acids (Calvo and Bennett, 2012). PNI also causes the release of Neuregulin-1 within the dorsal horn of the spinal cord and activation of ErbB receptors on microglia, which in turn stimulates the MEK/ERK1/2 pathway and plays a pivotal role in the microglial mitotic response and the development of neuropathic pain (Zhao et al., 2017). It is reported that nerve injury-induced hypersensitivity could be prevented by blocking microglial responses with minocycline in rats (Zhao et al., 2017). Compared to microglia, astrocytes appear to be important in maintaining neuropathic pain after PNI. Astrocytes are activated after exposure to pro-inflammatory stimuli secreted by activated microglia, such as interleukin-1β and tumour necrosis factor-α (Vergne-Salle and Bertin, 2021). Activated astrocytes increase the expression of monocyte chemoattractant protein-1 in the ipsilateral dorsal and ventral horns of the spinal cord as well as in DRG neurons through the JNK pathway, contributing to pain hypersensitivity after PNI (Vergne-Salle and Bertin, 2021). Therefore, PNI-induced microglia and astrocyte activations in the spinal cord are closely related to neuropathic pain, serving as important pain modulators.

Following PNI, neurodegeneration in the spinal cord is one of the known causes of the development of neuropathic pain (Finnerup et al., 2021). Degenerative changes including decreased neuron number and subsequent neuron death have been observed in the spinal cord after PNI, which is caused by retrograde cell atrophy and deprivation of distal targets (Duraikannu et al., 2019). It has been reported that approximately 50% of motor neurons in the lumbar spinal cord died within three weeks after sciatic nerve avulsion in adult rats caused by DNA damage-induced apoptosis through p53 regulation of the Bax gene (Martin and Wong, 2017). Various factors related to the individual (principally age) and the injury (such as the type and severity of the injury, region of the injury, type of involved neurons, time duration post-operation, and the subsequent therapeutic intervention) determine the extent of neuronal death. A conditioning lesion to the peripheral axons of adult neurons, which normally cannot regenerate central axons, may reactivate their regenerative ability and allow them to regenerate the subsequently damaged central axons (He and Jin, 2016). However, the decline in the ability of injured neurons to regenerate their axons due to declined supportive molecular responses, including the decrease of neurotrophic factors and receptors, growth-associated proteins, neurotrophins, transcription factors and relevant kinases, and some ion channels in the spinal cord and DRG, is one of the critical factors contributing to poor functional recovery after PNI.

Pain relief and nerve regeneration through peripherally administrated stem cell therapy targeting the spinal cord: Stem cell transplantation has been reported to provide several benefits in counteracting pathological changes in the spinal cord after PNI, such as pain relief and nerve regeneration (Trolle et al., 2014; Teng et al., 2019; Zhang et al., 2021). The previous study indicated that transplantation of boundary cap neural crest stem cells into the dorsal root avulsion site of both rats and mice caused cell migration in the spinal cord and the differentiation into neuronal phenotypes as well as gila, which promoted sensory axon regeneration (Trolle et al., 2014). In addition, 1 × 10^5 bone marrow stromal cells intrathecally injected into injured rats twice on postoperative days 4 and 5 accessed the spinal cord and inhibited the degeneration of dorsal horn neurons, which improved nerve regeneration and reduced pain after PNI (Teng et al., 2019). However, these sites of stem cell transplantation are neighboring the spine, away from the peripheral injury sites, and could cause additional adverse reactions, such as exposure to vertebral interspace and infection. In contrast, peripheral stem cell transplantation to the peripheral nerve injured site, in place of the locations close to the spine, could be a potentially safe and effective therapeutic strategy to achieve similar functional improvements while avoiding additional adverse reactions. Although rarely investigated, a previous clinical study transplanted human umbilical cord mesenchymal stem cells to the injured radial nerve of patients and observed improved recovery of muscle strength and touch and pain sensations in 80% of patients without adverse effects (Li et al., 2013), confirming the safety and tolerability profile of stem cell therapy for PNI. Our previous study has indicated that the peripheral administration of NCSCs prevented sciatic nerve defect-injury-induced spinal cord degenerative changes, improved the recovery of locomotor function, and relieved pain (Zhang et al., 2021). The peripheral administration of NCSCs improved the microenvironment for neuron survival and axon regeneration by increasing the expression of neurotrophic factors, such as growth-associated protein-43 and brain-derived neurotrophic factors (Zhang et al., 2021). In addition, PNI-induced spinal cord glial activations were attenuated by inhibiting NF-kB and ERK signaling pathways and reducing the expression of a pain-related factor, transient receptor potential vanilloid 1, which prevented mechanical allodynia and thermal hyperalgesia and relieved pain (Zhang et al., 2021).
in the treatment of various pathological conditions after PNI, such as spinal cord degenerative changes and neuropathic pain (Li et al., 2013; Trolle et al., 2014; Teng et al., 2019; Zhang et al., 2021). The safety of local administration of stem cells is one of the concerns, which restricts the clinical application of stem cell therapy. However, the prior clinical study employed local stem cell transplantation to patients without inflammation, infection, and hemorrhage, which minimized concerns regarding adverse effects (Li et al., 2013). This study provides evidence of the therapeutic benefit of peripheral stem cell transplantation to the injured site, away from the spinal cord, as a potentially safe and effective intervention for the treatment of PNI. Targeting PNI-induced spinal cord degenerative changes via peripheral stem cell transplantation could improve functional recovery and relieve neuropathic pain (Zhang et al., 2021).

While NCSCs were peripherally administrated via 3D printed nerve scaffolds in the prior study (Zhang et al., 2021), other peripheral administration routes would be able to be employed with similar benefits pending verification of future investigations. In addition, the sources of stem cells can come from various origins and be expanded from the induced pluripotent stem cells to the neural stem cells, as well as mesenchymal stem cells derived from adipose tissue, bone marrow, and umbilical cord (Jiang et al., 2017). While there is still much to learn about the therapeutic potential (safety, reliability, and maximum efficacy) of peripheral stem cell transplantation in PNI, developing more efficient regulations of NCSC differentiation into specialized neural cell lineages and avoiding tumorigenic risks require future investigations. The aging of stem cells is also an important concern, which is a common feature of all organisms, so it is critical to establish a system to detect the extent and proportion of the aging of stem cells to prevent aging-induced loss of function. After addressing these concerns, peripherally administrated stem cell therapy may become a clinically feasible and effective treatment after PNI in the future and improve patient quality of life, pending verification by subsequent clinical studies.

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