Review article

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Peripheral nerve injury: molecular pathophysiology and prospects for restorative treatment by means of cell transplantation: a literature review

Ziia K. Melikov, Volodymyr V. Medvediev

Department of Neurosurgery, Bogomolets National Medical University, Kyiv, Ukraine

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Address for correspondence:
Ziia K. Melikov, Department of Neurosurgery, Bogomolets National Medical University, 32 Platona Mayborody st., Kyiv, 04050, Ukraine, e-mail: melikov_ziya@ukr.net

Peripheral nerve injury (PNI) is a fairly common pathology—PNI accounts for 1-5% of all peacetime injuries and 12% of all combat injuries. This injury leads to disability, the development of chronic pain syndromes and a significant deterioration in the quality of life of the victims. Unfortunately, at present, in the case of the most frequent type of combat trauma — damage to the limbs — PNI treatment is mostly done last, "on the residual principle." Modern means of surgical and conservative treatment of PNI do not provide complete restoration of lost functions, therefore, restorative treatment of PNI is an urgent biomedical problem. The article reviews the currently known molecular mechanisms of various stages of PNI, as well as the plasticity of the central parts of the nervous system on the background of this injury. The main reasons for the limitation of autogenous recovery of functions after a sustained PNI are described — the absence of a relevant spatial organization of regrowth of axons in the area of PNI; post-traumatic death of neurons of spinal nodes and central parts of the nervous system; failure of plastic reconstruction of brain and spinal cord neural networks; irreversibility of atrophy of denervated muscles. Based on this, it was established that the means of restorative treatment of PNI should touch not only the epicenter of PNI, but also the central parts of the nervous system and denervated muscles. Mesenchymal stem cells (MSCs) are well-known means of a positive influence on the the restorative process in the focus of PNI, as well as a source of supportive influence/ strengthening effect and an amplifier of the plasticity of brain neural networks, which makes these cells a promising element of bioengineering treatment of PNI. The effect of MSCs on the central parts of the nervous system in case of PNI remains the least studied. Data from the literature indicate that such an effect can provide support for secondarily affected neurons and stimulate the plastic reorganization of brain networks, i.e., in general, significantly improve the results of restorative treatment of PNI.

Key words: *peripheral nerve injury; axonotomy; apoptosis; nerve regeneration; plasticity of neural networks; mesenchymal stem cells*

Epidemiology of peripheral nerve injury

Peripheral nerve injury (PNI) remains a common pathology, being one of the important causes of long-term or lifelong disability and impaired quality of life in many victims. This type of injury accounts for 1–5% of all peacetime injuries [1–3, 4, 6], and the annual incidence rate is 13–23 cases per 100,000 population [7, 13].

Due to the characteristic symptomatology of motor function deficits, as well as the high likelihood of developing chronic pain syndrome, PNI is associated with substantial financial costs [3, 5, 8, 14], which are increasing annually [8, 10]. This is influenced, among other factors, by the age and gender of the affected patients. Thus, patients with PNI in the USA are people aged about 38 years [10, 13], the male to female ratio among affected individuals is 3:1 [10, 13].

Upper extremity nerve involvement accounts for 81–90% of all cases of PNI [10, 14, 15]. The most common are lesions of the distal nerves of the upper extremities [13–15]. Only 10–19% of cases of peripheral nervous system injuries are on the nerves of the lower extremity[15–17].

In the early 2000s, at least 2.5–3.0 thousand cases of PNI were diagnosed annually in Ukraine, the average age of patients was 18–44 years. 60–75% of victims were diagnosed with disability [18]. According to our calculations, taking into account global epidemiological data, domestic epidemiological and demographic indicators, the cumulative number of disabled patients after undergoing PNI in the pre-war period in Ukraine should be about 270 thousand people [19].

In the structure of combat trauma, PNI accounts for about 12% of cases [20], and a number of factors

(traumatic disease, purulent-septic complications, lack of a differential approach to providing medical care) significantly worsen treatment outcomes of such patients [21, 22].

Challenges of modern means of surgical treatment of peripheral nerve injury

Despite advances in the development of effective surgical means for the treatment of PNI [12, 13, 20, 24–28], the outcomes (for various reasons) are far from satisfactory [19, 20, 23]. Hence, improving existing or creating new means is an urgent task.

Traditionally, nerve suturing (neurorrhaphy) has been the primary technical means of restoring peripheral nerve integrity [12, 20], in case of a significant defect — its plasty [29] or neurotization [30]. The greatest disadvantages are the considerable duration of such interventions, their dependence on additional equipment and surgeon's experience, additional trauma to the nerve during neurorrhaphy, negative effect of suture material on the regenerative process, significant probability of local inflammatory complications and suture failure, insufficient sealing of the nerve ends, which leads to aberrant nerve fiber growth with neuroma formation [23–25, 31]. Consequently, non-suture methods for connecting the ends of the transected nerve (chemical, photochemical, laser welding, electrowelding, etc.) are being actively developed [23, 31, 33–39], as well as microstructured and nanostructured bioengineering connectors containing cells, that will promote rapid sprouting of the injured site with vascular and nerve components [24, 40–42].

Pathophysiology of peripheral nerve injury

It is evident that further improvement of restorative treatment of PNI is impossible without considering the intimate mechanisms of the pathophysiology of this type of injury.

Reactions which are initiated by PNI affect not only the foci of trauma, but also remote ones associated with the damaged nerve — sensory and autonomic nodes, gray matter of the spinal cord, stem, subcortical, and cortical parts of the brain, as well as denervated muscles and other organs [45–49].

The main processes occurring in the focus of injury are the destruction of the distal part and the proximal part of the transected nerve, known as Wallerian degeneration [19, 43, 44]. Already within the first 30 minutes after transection, the largest segment of degeneration of the proximal part of the nerve is formed, within 8–24 hours — degenerative changes of the distal part occur [19, 43], and the whole process lasts about 1–2 weeks [19, 43].

Wallerian degeneration is initiated by a rapid increase in calcium ions concentration near the axonal membrane rupture, in particular due to the opening of axolemma cation channels [45] and the release of calcium ions from endoplasmic depots [45–49]. The wave of increased calcium ions concentration spreads to the cell body, causing histone deacetylase 5 (HDAC5) to be exported from the nucleus, which, by acetylating histone H3 molecules, enables the transcription of certain genes [46–48] ***(Fig. 1).***

The second, slower signal wave ***(Fig. 2)*** depends on the reverse transport of importin-β1 and vimentin proteins synthesized in axoplasm near the injury, which together with importin-α, NLS-bearing transcription factors (NLS — nuclear localization sequence) and phosphorylated protein kinase ERK1/ 2 (extracellular signal-regulated kinase 1/2) form a retrograde signaling complex associated with dynein [45]. After entering the soma, the components of this complex activate the transcription factor Elk-1 (ETS (E26 transformation-specific/erythroblast transformation specific) like-1) and also affect gene expression [45]. Another complex formed after axonotomy contains STAT3 (signal transducer and activator of transcription 3) transcription factor, importin-α, DLK (dual leucine zipper kinase) protein kinases, JNK (c-Jun N-terminal kinase) and JIP3 (JNK -interacting protein) factor and is transported in a dynein-dependent manner into the neuron body, where it activates the subunit of the transcription factor AP-1 (activator protein 1) c-Jun and ATF3 (activating transcription factor 3) [45–49].

The above transcription factors initiate the neuron's transcriptional response to damage [45–50]. In some cases, the described chain of reactions against the background of axonotomy-triggered calpain-dependent and ubiquitin-dependent axoskeleton degeneration [19,43] can be transformed into apoptotic cell death [19, 48].

At the same time, during the first minutes after axonotomy, the receptor tyrosine kinase ErbB2 (erythroblastosis oncogene B receptor tyrosine kinase 2) of neurolemocytes activated by neuroligins of the axolemma initiates the MAPK cascade (mitogen-activated protein kinase), and by the end of the 2nd day, myelin formation stops [19, 43].

Due to LIF (leukemia inhibitory factor) and MCP-1 (monocyte chemoattractant protein 1) factors, which are expressed by activated neuroleumocytes, as well as due to antibodies to myelin, complement factor C5, and type VI collagen, macrophages are involved at the site of injury [19, 43, 51–53], not only resident, but also peripheral from the 4th day [19, 43, 51, 52]. In general, macrophages of the M1 fraction are involved in the degeneration of the peripheral part of the injured nerve and development of the local inflammatory process, whereas macrophages of the M2 fraction have anti-inflammatory properties and participate in the process of axon regeneration [19, 52], in particular in the attraction and promitotic stimulation of Schwann cell precursors [53]. Another important role of macrophages on the background of PNI is local stimulation of angiogenesis [53].

The above transcription factors also activate the neuron regenerative program [45, 48, 54]. Regenerative axon growth depends on numerous extracellular factors, in particular, on the surface proteins of Schwann cells, pericytes, endotheliocytes, and fibroblasts, as well as on the proteins of the newly formed intercellular substance [19, 48, 55, 59, 60].

This article contains some figures that are displayed in color online but in black and white in the print edition

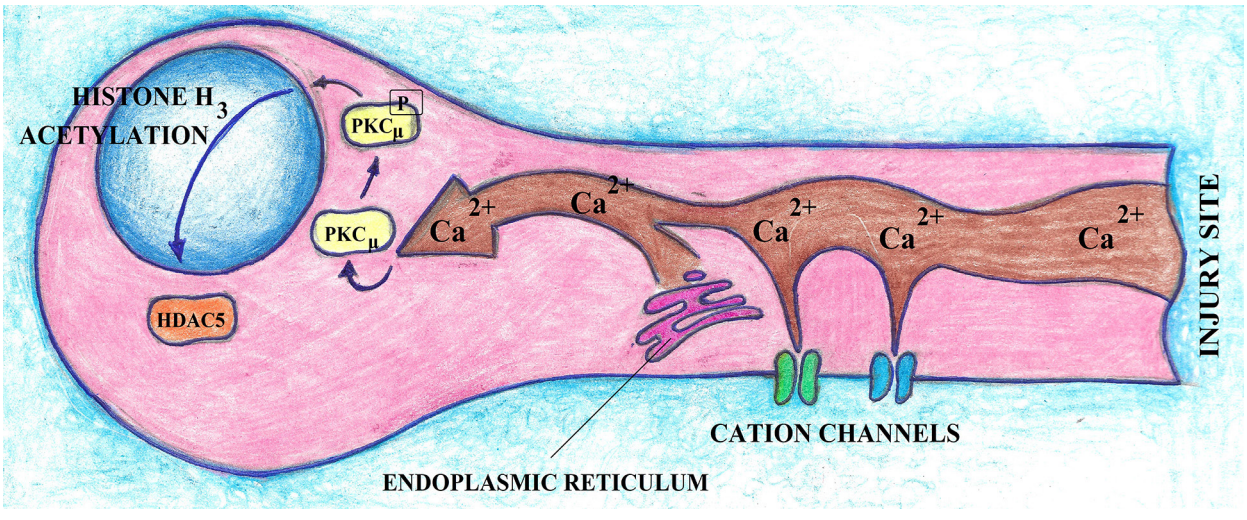

Fig. 1. The first wave of cerebripetal signaling after axonotomy: increase in calcium ion concentration near axonal membrane rupture, activation of PKCμ (protein kinase Cμ), which enables nuclear export of histone deacetylase (HDAC5), leading to histone H3 acetylation and expression of numerous regulators of the cell's response to axonotomy

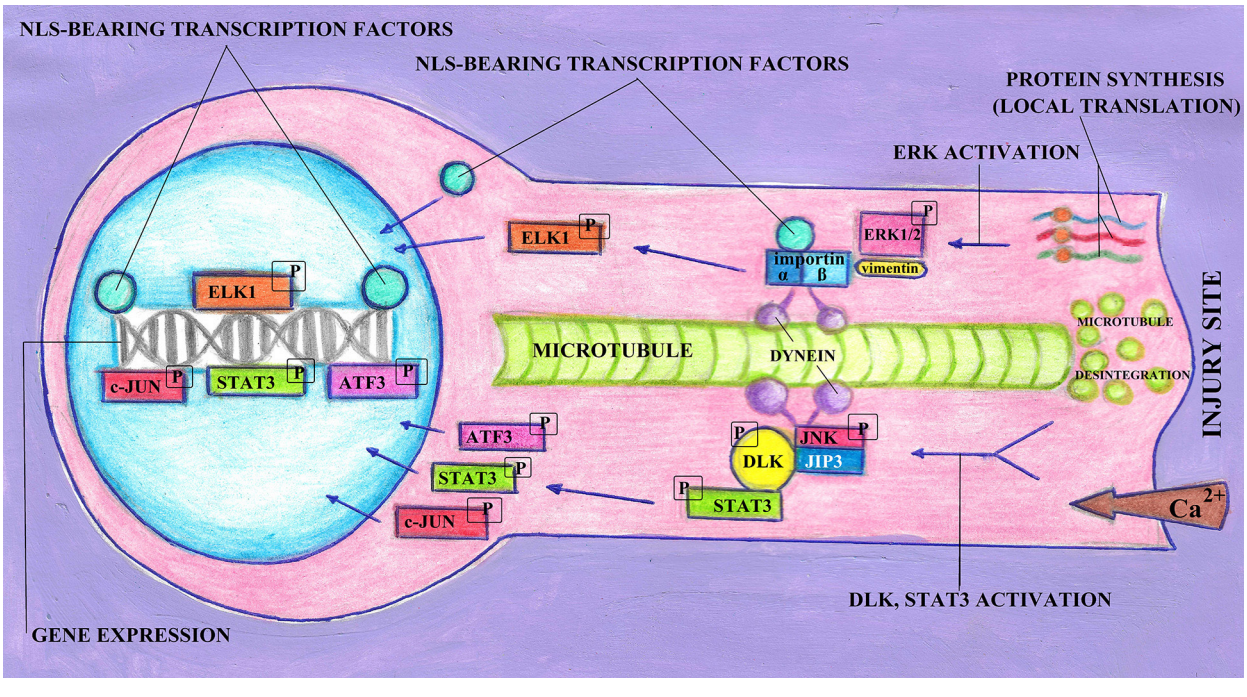

Fig. 2. The second wave of cerebripetal protein signaling after axonotomy (explanation in the text)

Loss of spatial contact with degenerating axons is an important promitotic factor for neuroleumocytes, which is implemented by many intracellular and extracellular factors [56, 57], in particular, a neuregulin-1-dependent cascade [51, 56–58]. Due to the existence of endoneurial remnants, immature neurolemocytes form the so-called Büngner bands, that direct the axons growth by a number of adhesion factors, for example, laminin and ninjurin-1 [19, 43, 48, 54]. The expression of other axon growth regulators by activated neurolymocytes, macrophages, and fibroblasts of the distal part of the injured nerve has also been described [43, 48, 54, 55].

Neuroplasticity and apoptosis in the central parts of the nervous system against the background of peripheral nerve injury

The state of premotor neurons of the cerebral cortex and motoneurons of the spinal cord is crucial for the success of the recovery process following motor nerve injury [61–64]. PNI is thought to predispose selective remodeling of cortical synapses, associated with ascending degeneration of processes of sensory and motor neurons and their sporadic death [65–70]. As a consequence, cortical areas deprived of normal afferentation are covered by network effects of

neural networks of neighboring areas [70]. A possible mechanism of such remodeling is the collateral growth and formation of synapses by the processes of neurons of neighboring cortical areas, revealing of the so-called hidden interneuron connections within the area deprived of usual afferentation [63, 69, 71].

As a result of axonotomy, the volume of the neuron body increases, the nucleus moves to the periphery against the background of chromatolysis [65, 66], which is associated with the active synthesis of proteins involved in the remodeling of neuron connections and axonogenesis [72, 73]. Rapid initiation of the neuroplastic process after PNI in an adult is observed in the spinal cord, rostroventral part of the medulla oblongata, locus coeruleus, nuclei of the dorsal columns and suture, periaqueductal gray matter, thalamus, and sensorimotor cortex [67, 69, 70, 74].

In some cases, axonotomy triggers apoptosis of spinal cord motoneurons by increasing the expression of APAF-1 (apoptotic protease activating factor 1), Bax (B-cell lymphoma 2 associated X protein), caspase-3, and caspase-9 [75–77]. Under the same conditions, necrotic changes are observed in the gray matter of the spinal cord against the background of increased tissue glutamate concentration and decreased cAMP content [77]. The consequences of widespread death of spinal cord neurons are reactive gliosis [62, 77–80] and reorganization of the neural circuit of the motor system.

In general, remodelling of brain neural networks on the background of PNI is the most probable mechanism for changing their functional topology [79, 81–83]. Consequently, the success of the regenerative process at PNI largely depends on the quality of this plastic process.

Limitations of regeneration in peripheral nerve injury and ways of their elimination

Despite the high autoregenerative potential of the peripheral nervous system, PNI is a frequent cause of deep paresis, neuropathic pain syndromes, and disability [13, 26, 31, 64]. It can be argued that despite the use of modern methods of diagnosis and treatment, the recovery of lost functions of the injured nerve is limited in most cases [19,23,65–70]. This is due to at least 4 reasons:

1) difficulty and lack of proper spatial organization of axon growth in the PNI area [37, 38];

2) postaxonotomy and secondary death of neurons of spinal nodes, spinal cord and brain [65–71, 78];

3) limitation of plastic reconstruction of brain neural networks and spinal cord after PNI [69, 74, 84];

4) irreversible atrophy of denervated muscles [20, 79, 85, 86].

Consequently, three types of interventions can improve the results of the recovery process on the background of PNI:

1) improving conditions for axonal sprouting in the PNI area [24, 40–42, 86–89];

2) preventing postaxonotomy and secondary neuronal death and stimulating the neural networks plasticity [90–93];

3) preventing the death of muscle fibers and maintaining their plasticity [85, 86].

The development of means of the first type is associated with the improvement of technologies for connecting parts of the injured nerve [23, 31, 33–36, 37–39] and the creation of tunneled bioengineered implants, often in combination with various types of undifferentiated cells and growth factors [24, 40–42, 86–89, 94].

Means of the second type should provide a ubiquitory effect on brain neural networks and spinal cord, for example, by factors producing stem cells [90–92] or against the background of physical neurorehabilitation programs [93], etc.

Intramuscular transplantation of stem cells or their progeny [87], physical neurorehabilitation effects [95], etc. should be considered as means of the third type.

Mesenchymal stem cells in the treatment of peripheral nerve injury

Mesenchymal stem cells (MSCs) are a type of stromal cells with the potential to give rise not only to similar cells, but also to progenitors capable of differentiating into fibroblasts, osteocytes, chondrocytes, adipocytes, etc. [90–92]. The most common sources of MSCs are adipose tissue, bone marrow, placental tissue, umbilical cord, umbilical cord blood, and dental pulp [92, 96].

The multifaceted beneficial effect of MSCs is attributed to pathotropic homing [97], the phenomenon of neurogenic transdifferentiation [90, 97–99], particularly in neurolemocytes [100–102], the ability to fuse with recipient cells [103], microvesicular [104–108], factor [97, 100–102] or contact [97, 105] influence. In addition, transplanted MSCs exert immunosuppressive and probably local anti-inflammatory effect [109–112].

In PNI, MSCs or their derivatives are most often used in combination with bioengineering matrices [24, 40–42, 88–89, 94]. For example, implantation of a silicone tube filled with a suspension of MSCs into the area of a rat sciatic nerve defect improves the functional-anatomical and morphological indicators of motor function recovery of the paretic limb [94, 113, 114]. Mesenchymal stem cells derived from visceral adipose tissue and associated with fibrin matrix improve the regeneration of an injured nerve and the motor function recovery [89], promoting, among other things, to the survival of sensory neurons in spinal cord nodes [88, 89]. Such effects of MSCs are associated with differentiation of these cells into neuroleumocytes and their production of growth factors, in particular BDNF (brain derived neurotrophic factor), CNTF (ciliary neurotrophic factor) and FGF-2 (fibroblast growth factor 2) [100–102].

Mesenchymal stem cells are one of the traditional objects in the development of therapeutic agents affecting the structures of the CNS, for example, in chronic inflammatory and degenerative diseases [115, 116]. In Alzheimer's disease and ischemic stroke, transplantation of MSCs or medium conditioned by these cells is accompanied by antiapoptotic effect, modulates the inflammatory process, stimulates axons growth and neurogenesis [117–120], generally improving the neurological status of patients. In addition, intrathecal administration of MSCs or conditioned medium improves motor function recovery against the background of experimental spinal cord injury, most

likely due to potentiation of the neuroplastic process [108, 121]. Taking into account the above, intrathecal transplantation of MSCs on the background of PNI can be regarded as one of the means of supporting and proneuroplastic influence on brain neural networks, representing a promising means of restorative treatment of PNI consequences ***(Fig. 3)***.

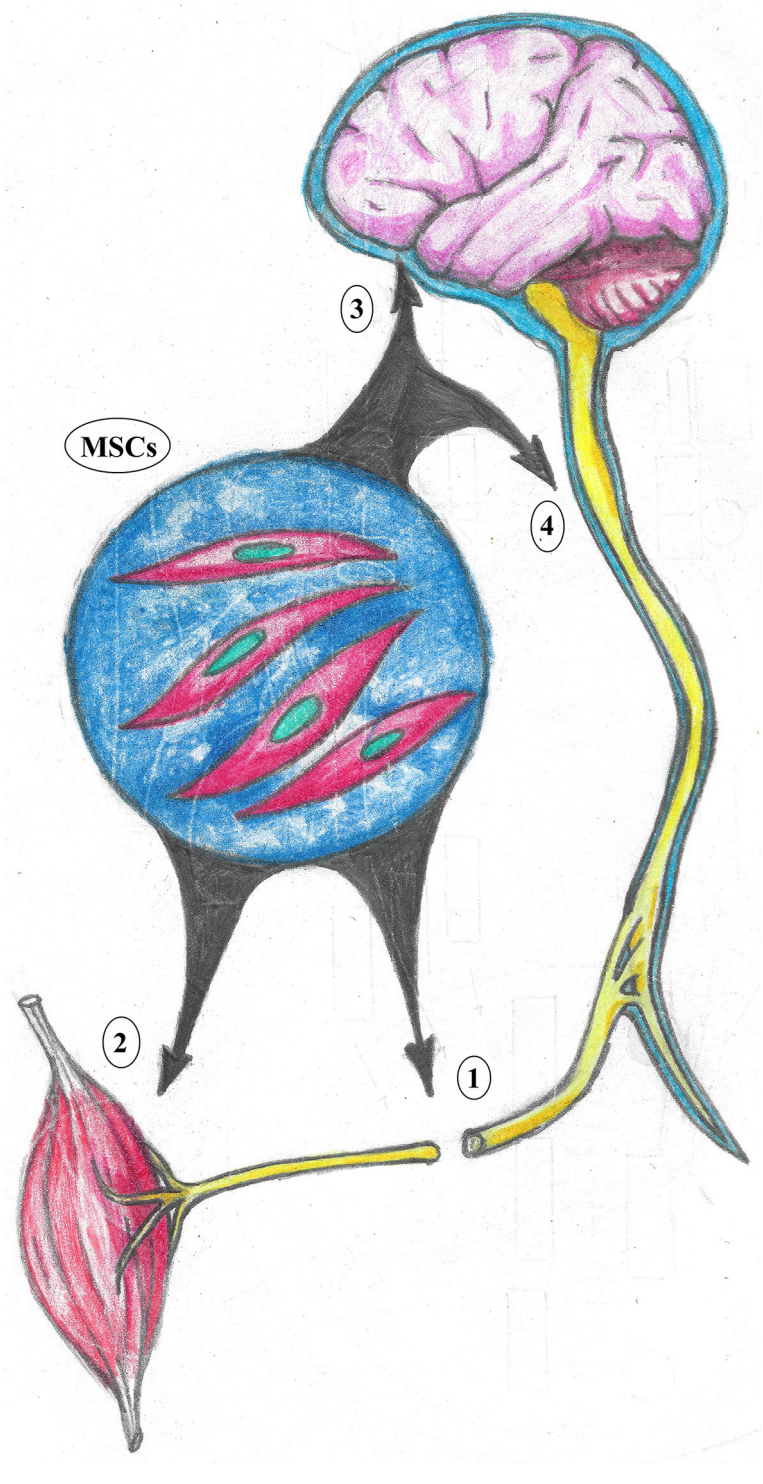

Fig. 3. Possible areas of using MSCs properties to enhance the regenerative process on the background of PNI: 1 – epicenter of peripheral nerve injury (PNI); 2 – denervated muscle; 3 – brain; 4 - spinal cord

Conclusions

Peripheral nerve injury is one of the leading causes of disability and associated economic costs. The reason for this situation is incomplete restoration of injured nerve function due to incomplete axon growth at the injury site, neuronal death in the central and peripheral parts of the nervous system, and atrophy of denervated muscles. Improving the results of PNI restorative treatment depends significantly not only on the improvement of means of influencing the regenerative process in the epicenter of the injury, but also on the development of means of positive influence on neural networks of the brain and denervated muscles. Since MSCs are the most accessible and most widely tested bioengineering tool for influencing neural networks [100–102, 115, 116, 121], their intrathecal transplantation on the background of PNI can have a substantial positive impact. Further research is needed to explore this potential.

Disclosure

Conflict of interest

The authors declare no conflicts of interest and no personal financial interest in the preparation of this article.

Ethical guidelines

This article contains no studies involving humans or animals.

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