The best of both worlds: mastering nerve regeneration combining biological and nanotechnological tools

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Over the last decade, remarkable developments in nanotechnology have powered medical research, unlocking novel approaches for regenerative medicine and health issues such as the treatment of traumatic peripheral neuropathies.

With an estimated incidence of 13 to 23 cases per 100,000 people in developed countries, traumatic nerve injuries constitute the most frequent type of peripheral nervous system (PNS) damage. Peripheral nerve regeneration results from a complex cascade of events associated with everyday activities such as sports, work, recreation, and driving. Upon injury, the connection between the neuronal distal axon and soma and, finally, the regenerated axon triggers a cascade of cellular events which lead to the reinnervation of the target organ. On the other hand, non-surgical approaches such as physical exercise can be a suitable option all along treatment (Armadada-Silva et al., 2013), but electrical stimulation seems to have an optimal treatment window – between the first 21 days after damage – to yield good clinical results (Su et al., 2018). Even so, functional recovery remains a clinical challenge.

Perspective

Even though the use of MNP for different applications is widely disseminated, their toxicological profile has not been well defined yet in the context of a repair intervention. When MNP internalization by cells is required, nanocytotoxicity must be carefully considered for MNP validation as a biomedical tool. Moreover, MNP cytotoxicity is dose-dependent, and the generation of reactive oxygen species is chiefly responsible for cell damage. For these reasons, the evaluation of iron levels is of great interest for the use of MNP in regenerative medicine applications.

In addition, special attention should be given to the analysis of the MNP degradation process. MNP degradation depends on oxygen storage, metabolism, and proliferation rate, and inherent MNP factors such as size, coating, and shape. Iron oxides and MNP degradation pathways vary, with the latter being either incorporated into hemoglobin or join the native iron pool of the body and are degraded by normal iron-recycling pathways. However, iron doses can affect cell morphology, signaling processes, and differentiation potential. Nevertheless, MNP use in controlled conditions allows their efficient internalization by cells without affecting cell functions or differentiation capacity.

As mentioned above, a crucial step in PNS regeneration is the successful delivery of cells to the target site and their reattachment in order to overcome these obstacles, our group has improved cell therapy outcomes through the implementation of magnetic targeting of AdMSCs for the treatment of peripheral nerve injuries (Fernández et al., 2021). Magnetic targeting is an encouraging method for the treatment of CNS and PNS lesions, as it optimizes the rates at which systemically transplanted cells arrive and remain at the site of injury. This brings about an increased concentration of trophic factors secreted by AdMSC, which improves cell immunomodulatory effects. Moreover, magnetic targeting allows the in vivo remote manipulation of transplanted cells using small magnets. This approach avoids the invasive nature of cell transplantation or an extra surgical procedure that could per se promote an inflammatory reaction and the elongation of regenerative processes, including AdMSC magnetic targeting, also allows cell transplantation in the acute phase after lesion. Given the regenerative potential of lesions in the PNS is short and represents a critical point in neuroregeneration processes, acute phase transplantation may contribute to more satisfactory results.

Good results using magnetic targeting have been reported for the treatment of CNS lesions (Grayston et al., 2022). Also, employing spinal cord injury models, different authors have demonstrated that MNC labeled with MNP responded to the applied magnetic field and, more relevant, improve motor function (Kowalik et al., 2018). Some studies have reported the use of magnetic targeting to deliver growth factors to the injured sciatic nerve (Fernández et al., 2018), which confirmed the use of MNC in the treatment of peripheral nerve injuries (Fernández et al., 2018). Recently, in a rat model of sciatic nerve lesion 2 weeks after, the efficacy of AdMSC magnetic targeting to speed up nerve regeneration from a morphological and functional point of view has been demonstrated. This approach uses a hybrid material consisting of AdMSC loaded with 10 nm iron oxide MNP in their endosomes and submitted to the force produced by an external Neodymium Iron Boron magnet, which warrants animal comfort and full mobility during treatment (Soto et al., 2021). Therefore, to the best of our knowledge, and despite the encouraging results provided in previous studies, a hybrid approach combining the two strategies for in vivo sciatic nerve regeneration has so far only been reported by our group.
Hybrid materials have proven useful, and the combination of different properties improves the therapeutic outcomes for numerous CNS and PNS injuries. Beyond the encouraging results, several challenges must be met prior to the translation of magnetic targeting to clinical applications. Some of them are optimal conditions for cell magnetic targeting – including thorough studies of the bio-nano interphase (MNP and biological environment interaction) – and the interaction between magnetically loaded cells and the magnetic fields applied once cells are intravenously administered. Another pressing need is the evaluation of MNP applied once cells are intravenously administered. This technique has proven useful to improve and accelerate remyelination and distal latency recovery after injury in an animal model. AdMSC: Adipose-derived mesenchymal stem cell; GM-CSF: granulocyte-macrophage colony-stimulating factor; MNP: magnetic nanoparticles.

Figure 1  Summary of the relevant molecular events associated with the Wallerian degeneration process in the peripheral nervous system and therapeutic strategies for traumatic injuries. (A) Scheme of the in vivo degenerative-regenerative process. Sciatric nerve scheme showing a control nerve made up mainly of axons, connective tissue, denervating Schwann cells (SC), and resident macrophages (RM). After the injury, the proximal stump of the nerve remains connected to the neuronal soma and preserves its structure; otherwise, the distal stump suffers a degenerative process after the lesion. SC lose their myelinating phenotype and proliferate, becoming repair Schwann cells (r-SC) which, together with RM, secrete cytokines and recruit hematogenous macrophages (HM). HM contributed to the removal of axon and myelin debris, while Bungner bands generated by r-SC guide axon regrowth to reinnervate the target site. At the same time, axons and SC reestablish the cilostlast and SC recovers its mature myelinating phenotype. (B) Temporal progression of cytokine secretion during degeneration. Within the first hour after injury, SC begin to secrete pro-inflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-1β] which, together with factors secreted by fibroblasts, recruit HM which arrive at the site of injury 2–3 days post-injury. After the arrival of HM, the second stage of the inflammatory response begins, characterized by the second peak in IL-6 and a peak in IL-10, an anti-inflammatory cytokine, around 7 days post-injury. This event coincides with the peak in HM recruitment. Adapted from Rotshenker (2011). (C) Therapeutic strategies for traumatic peripheral nerve injuries. Conventional strategies (right) range from microsuture to nerve grafts and polymer conduits in more severe injuries where the nerve is completely transected. In less severe lesions, pharmacological therapy is commonly used for neuropathic pain treatment. In both cases, physical exercise and electrostimulation are used to improve regeneration and alleviate pain symptoms. Conventional strategies sometimes fail in restoring normal function and morphology of the nerve, which is why non-conventional strategies (left) such as cell therapy alone or combined with magnetic targeting have been developed over the last decades to improve cell recruitment to the injured nerve. The innovative hybrid therapeutic strategy appears as a promising tool to reach complete neuroregeneration after traumatic injuries. This technique has proven useful to improve and accelerate remyelination and distal latency recovery after injury in an animal model. AdMSC: Adipose-derived mesenchymal stem cell; GM-CSF: granulocyte-macrophage colony-stimulating factor; MNP: magnetic nanoparticles.