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EDITORIAL

How can neuroplasticity be utilized to improve neuropathy symptoms?

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A broad variety of diseases and conditions ranging from traumatic, inherited, autoimmune, toxic, and metabolic ones can affect the peripheral nerves [1,2]. Depending on the distribution and on the type of nerve fibers involved, peripheral neuropathies can be classified as mono- or polyneuropathies, and more important, as sensory, motor, and/or autonomic [3]. Despite the different triggering sparks, peripheral neuropathies frequently share some common signs and very disabling symptoms which include numbness and tingling in feet and/or hands, lack of coordination, and muscle weakness or paralysis. The occurrence of a sharp or burning pain, frequently also accompanied by hyperalgesia and allodynia, is not uncommon [3]. Since so many causes can lead to their rise, peripheral neuropathies are very common, and for the same reason, they are often difficult to be investigated, diagnosed, and overall effectively treated.

In fact, the current treatments for peripheral neuropathies are essentially based on the elimination of the triggering cause (an option not always available), or simply palliative, aimed to relieve the most disabling painful symptoms, by the use of pain killers such as opioids, antiseizure medications, capsaicin, and antidepressants [4]. Alternative, nonpharmacological approaches used to help easing the neuropathic symptoms may be represented by transcutaneous electrical nerve stimulation [5].When an inflammatory condition is present, plasma exchange and intravenous immune globulin administration are effective options [6]. However, improving nerve fibers reparation still remains a challenging aim. But to which extent repair is effective after nerve damage? And, is it really possible to effectively boost the limited regenerative properties of the nervous system thus translating the concept of neuroplasticity into clinical therapies?

Neuroplasticity is defined as the ability of the nervous system to adapt both to intrinsic changes and to environmental stimuli by changing its structure and its function, and to properly respond to toxic stimuli by regenerating itself [7]. Once considered just a theoretical possibility, neuroplasticity has now been largely demonstrated to be a phenomenon occurring physiologically. However, in pathological conditions, this system frequently fails to effectively work, and the neuroplasticity changes often result insufficient to repair a severe damage, sometimes even further worsening the situation. An intriguing therapeutic challenge in neuroscience research is to identify molecules and/or mechanisms able to stimulate neuroplasticity, with the aim to drive it to repair the nervous damage.

Many options are now under investigation, and several studies have explored this possibility in different fields, thus identifying a set of molecules and cells as putative targets. Among them, brain-derived neurotrophic factor (BDNF) has been demonstrated to be a pivotal 'driving force' in several models, both of central and peripheral nervous system [8]. This neurotrophic factor is essential for central physiological plasticity, but increasing evidence supports its role also for peripheral nerve damage [8]. An important role in the pathogenesis of neuropathy-related symptoms has been recently assigned to spinal microglia, since it is able to react to a nerve injury by activating molecular changes that eventually lead to neuropathic pain [9]. Among the different cellular pathways purinergic receptors, mitogen-activated protein kinases family, and the complex PTEN/mTOR have often been reported to be strictly related to neuroplasticity changes, thus suggesting they could represent putative targets for neuroplasticity enhancement [10]. Interestingly, all these molecular targets can individually direct neuroplasticity toward a regenerative mission. But could their effect be synergistic if properly stimulated? This is a very intriguing, unanswered question, since the identification of a multiline action could lead to an amplification of their effect, with a more promising possible translation in clinic. Under this perspective, a leading role may be played by mesenchymal stem cells (MSCs), due to their many-sided properties which are somehow linked to all the previously described targets [11]. In fact, MSCs are adult stem cells derivable from different organs, such as bone marrow or adipose tissue, and they are characterized by several peculiar abilities, including their capacity to release trophic factors, such as BDNF [12], to switch microglial activation [13] and to regulate immune cell activation [14].

Moreover, MSCs have been suggested to be directly able to positively influence neuroplasticity, since they promote and boost endogenous neurogenesis, neuronal survival, differentiation, and neurite elongation, also after the exposure of neuronal cells to a toxic stimulus [15,16]. So the next question is, how could this approach be applied to peripheral neuropathy research?

With respect to other pharmacological options acting on symptoms, MSCs would have the advantage, besides being of autologous source, to act on the nerve injury site, trying to

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counteract the damages and to restore the correct environmental and molecular pathways. Moreover, the already reported ability of MSCs to spontaneously migrate toward a lesion site [17] could make easier to deliver the needed factors. In addition, the possibility to obtain engineered MSCs gives a further chance, since in many cases the nerve regeneration is hampered by the glial cell-dependent release of inhibiting factors, such as NOGO and MAG, known to promote in the adult a scar formation rather than the correct nerve myelination and regeneration. Some authors demonstrated that MSCs can spontaneously release, or can be forced to release, some factors creating a less inhibitory milieu for nerve regeneration [18]. The preliminary results obtained by several authors are very encouraging since MSC were effective in different models, protecting neurons and nerve fibers from degeneration and improving the functional recovery [19]. In addition, many efforts are underway in order to identify culture conditions able to further potentiate the MSC regenerative potential, or even more to identify bioactive molecules (such as microRNAs) aimed to address the MSC action toward a specific step of the regenerative/reparative process [18], thus paving the way to a possible and feasible use of MSCs to force neuroplasticity.

Anyway, a final caveat must be taken into account when treating the neuroplasticity theme, since although this process can be undoubtedly exploited to 'repair' or to counteract a damage occurring in the nervous system, it must be considered that 'maladaptive' neuroplastic rearrangement often leads to develop neuropathic symptoms, one for all chronic neuropathic pain [20]. In this way, neuroplasticity manipulation could represent a double-edged weapon, and very rigorous and in-depth analysis should be performed to ascertain the feasibility of this option.

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Declaration of interest

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