PERSPECTIVE

Neural prostheses for restoring functions lost after spinal cord injury

Spinal cord injury (SCI) is a debilitating condition that affects more than 2.5 million individuals worldwide (Thuret et al., 2006). In addition to its devastating effects on the individual, this disease is a heavy burden to the society in terms of health care costs, which are estimated in billions of dollars annually in most developed countries (Cadotte and Fehlings, 2011). This disorder is typically classified into complete and incomplete SCI. Individuals suffering from a complete SCI have little prospect of rehabilitation, whereas motor recovery can still take place in patients with incomplete SCI. Damage to the spinal cord can lead to a variety of different outcomes, depending on the severity and location of the injury. For instance, high cervical lesions lead to paralysis of the four limbs (tetraplegia), whereas lower lesions lead to paralysis of the lower part of the body (paraplegia). The majority of patients with SCI also experience complications such as respiratory infections, urinary tract infections, cardiovascular diseases, as well as comorbid psychiatric symptoms related to depression and anxiety (Ullrich et al., 2014). At the molecular level, SCI causes biochemical changes leading to the death of a variety of cells, including neurons and astrocytes. Ongoing demyelination and apoptosis of oligodendrocytes are also commonly observed following damage to the spinal cord (Thuret et al., 2006). One of the key events mediating motor recovery in patients with SCI is neural regeneration, which occurs during the first days after injury and can take months to years to fully develop (Raineteau and Schwab, 2001). Primates and humans subjected to spinal cord hemisection lesions typically exhibit an extensive ability to recover volitionally guided locomotion due to spontaneous plasticity of corticospinal axons at the level of the injury (Rosenzweig et al., 2010). In the past few years, continued research in the field of neural regeneration has helped researchers identified specific targets that may mitigate the symptoms of SCI and promote long-term functional recovery (Fakhoury, 2015). However, despite the tremendous growth in the number of nonoperative and operative treatment strategies, neural regeneration and functional recovery after damage to the spinal cord remains very limited. This field of research would clearly benefit from ongoing development of new therapeutic approaches that could facilitate functional rehabilitation in paralyzed patients.

Functional and neuroanatomical findings from the past few years strongly suggest that spontaneous plasticity after SCI can be potentiated by specific experimental manipulations. More particularly, the use of neural prostheses (NPs) has shown great promise for the treatment of SCI by promoting appropriate neural activity in otherwise disordered circuits (Mondello et al., 2014). NPs are assistive devices that use electrodes to directly interface with the central nervous system. By providing local stimulation at various parts of the spinal cord, they help promote host tissue regeneration and plasticity. **Figure 1A** describes how NPs could be used to restore damaged connections and promote the recovery and voluntary movement following SCI. In most existing devices, the electrodes used for electrical stimulation are either attached to the surface of the skin over nerves or directly implanted into the central nervous tissue. Implanted NPs are usually more successful in delivering local electrical stimulation, and appears to be clinically effective in providing the ability to perform complex motor movements in individuals with paraplegia or low tetraplegia. A typical implanted device comprises of a microarray electrode coupled to a battery that produces electrical pulses. Specific electrophysiological requirements need to be considered when designing such devices. For instance, the coating material needs to be biocompatible with the spinal nerve tissue, and the battery used should work without external source for at least 10 years without replacement. Recently, researchers from the Swiss Federal Institute of Technology in Lausanne have developed a new spinal cord implant called the e-dura implant (Minev et al., 2015). Unlike most implants, the e-dura implant is made of material with elastic properties that help reduce friction and inflammation when implanted in the spinal nerve tissue. Moreover, because the e-dura implant has physical and mechanical properties matching the statics and dynamics of host tissues, it remains functional for a long period of time within the spinal cord (Minev et al., 2015). However, despite its proven efficiency in animal models of SCI, its long term biocompatibility and functionality still need to be tested in human clinical trials.

Recent articles published by myself and other groups have discussed the potential of electrical stimulation in restoring motor function following an incomplete injury to the spinal cord (Grahn et al., 2014; Fakhoury, 2015). This technique is already in clinical use, and has been shown to significantly increase the survival of neural cells at the level of the injury. Electrical stimulation of the spinal cord is known to promote the expression of certain genes and neurotrophic factors that make neurons more resistant to stressful conditions (Mondello et al., 2014). By allowing the recruitment of significantly higher amount of motor units, stimulation of the spinal cord provides more benefits than functional electrical stimulation of muscles (Grahn et al., 2014). This could help mediate neuroplastic changes within the spinal cord circuit. Spinal cord stimulation also constitutes an important tool to regulate numerous components of the central nervous system, including the critical barriers to neuronal survival, differentiation, and synaptogenesis (Mondello et al., 2014). In addition, spinal stimulation has shown to increase the ability of intact corticospinal axons to sprout after SCI, thus promoting neural regeneration and facilitating functional recovery in paralyzed patients. Several methods have been developed for the stimulation of the spinal cord. Among them, epidural stimulation is well established and constitutes a safe treatment for chronic pain. This method relies on the implantation of an array of electrodes over the dorsal surface of the spinal cord (Fakhoury, 2015). Recently, it was shown that neuromodulation of the spinal circuitry through epidural stimulation can help individuals with SCI regain voluntary control of paralyzed muscles for brief periods of time (Grahn et al., 2014). Although promising, still more work need to be done before evaluating its feasibility and efficiency in large clinical trials. On the other hand, intraspinal microstimulation uses electrodes that penetrate the spinal cord for focal stimulation of spinal circuits in the intermediate and ventral regions of the grey matter (Mondello et al., 2014). Although this method requires more invasive surgery than epidural stimulation, it offers a higher degree of control over voluntary movements in paralyzed patients.

Nowadays, scientists are designing NPs that could provide both electrical and chemical stimulation to the spinal cord. By integrating microfluidic channels within NPs, specific volumes of pharmacological agents could be delivered to the spinal cord for extended durations. Such approach has already been tested in

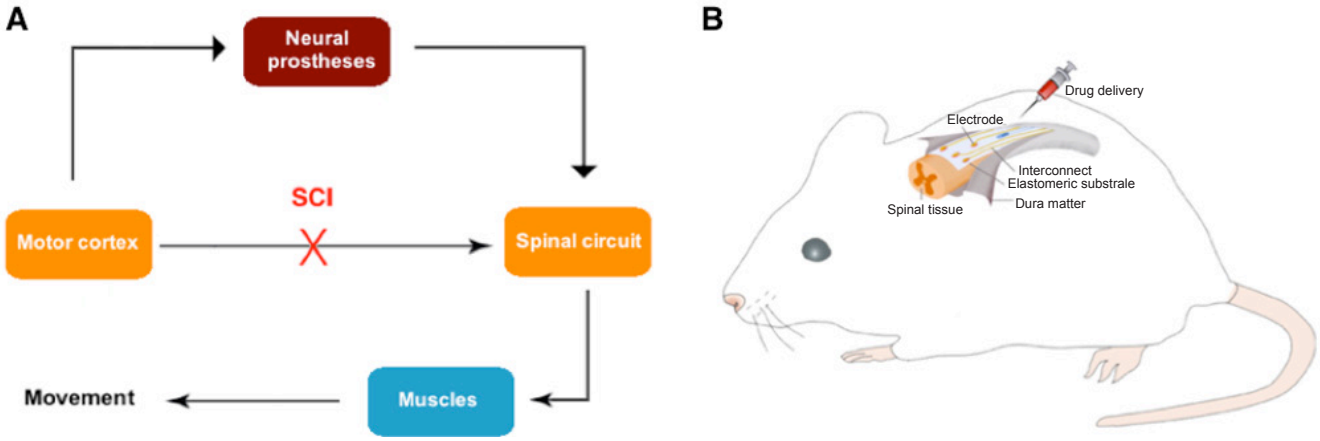

Figure 1 Therapeutic application of neural prostheses (NPs).
(A) NPs can replace injured descending connections and restore voluntary movements following damage to the spinal cord. (B) Schematic illustration of a neural prosthesis implanted on the surface of a rat's spinal cord. The implanted device can deliver electric impulses for long period of times without causing damage or inflammation to the surrounding tissues. The device also contains microfluidic channels that could be loaded with pharmacological substances used for local delivery to the spinal cord.

animal models of SCI in a recent study from researchers at the University of Zurich, which showed that it's possible to restore the functions of the injured spinal cord by using both electrical and chemical stimuli (van den Brand et al., 2012). In their study, adult rats received lateral hemisections of the spinal cord at thoracic levels, and as a result, were completely paralyzed from the hindlimbs. Although this intervention leads to the interruption of direct supraspinal pathways, it normally leaves an intervening gap of intact tissue in the spinal cord, thus mimicking the physiological nature of injury observed in patients with SCI (van den Brand et al., 2012). Following SCI, rats were implanted with a NP that could systematically provide electrical and chemical stimuli to the vicinity of the spinal cord (**Figure 1B**).The chemical stimuli consisted of a cocktail of monoaminergic agonists to dopamine, epinephrine and serotonin receptors within the spinal cord. Such pharmacological manipulation usually leads to rapid changes in synaptic efficacy, which in turn improves the regeneration of damaged pathways after SCI. The injection of chemical agents was followed minutes later by localized epidural stimulation to motor neurons. Through the combined effect of spinal stimulation and training with a vertical support system, rats that were suffering from paralysis of the lower limbs were able to regain their locomotor activity within weeks of exercise (van den Brand et al., 2012). The results of this study are very promising, and could constitute a first step towards restoring voluntary movements in paralyzed patients.

In summary, NPs can be used to promote axonal growth and the expression of several genes known to regulate neuronal survival and differentiation. Through the use of both electrical and chemical stimulation of the spinal cord, implanted NPs have shown to significantly enhance axon sprouting and regeneration. Although animal studies have yielded crucial information regarding the therapeutic efficiency of NPs, they need to be completed by clinical studies to derive full benefits from their results. The changes observed in animal models of SCI could be of interest in the clinic if they are sufficiently important to eventually restore the control of voluntary movements in paralyzed patients. Hopefully, future work will lead to the development and implementation of next-generation NPs that could restore functions lost after SCI and significantly improve the quality of life of paralyzed patients.

Marc Fakhoury*

Department of Neurosciences, Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada

***Correspondence to:** *Marc Fakhoury, B.Sc., M.Eng., marc.fakhoury@umontreal.ca.*
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