COMMENTARY

Repairing the injured spinal cord: sprouting *versus* regeneration. Is this a realistic match?

The article by Meves and Zheng (2014) is addressing a continuous shift in the field of spinal cord injury (SCI) research that has occurred over the last century. Before that, the spinal cord was viewed as "hard wired" and treatment considerations were based on observations that axons in the periphery were able to regenerate, but those in the central nervous system (CNS) were not (David and Aguayo, 1981). This led to the suggestion that it is the CNS environment that inhibits neurite growth, which initiated a quest to identify the growth inhibitory factors in the CNS (Caroni et al., 1988). The ultimate goal was to neutralize these factors in order to enable regeneration of injured axons, potentially over long distances. More recently, however, the research focus has shifted to study more natural repair mechanisms that fall under the relatively broad term of neuro-plasticity (Fouad and Tetzlaff, 2012). Injury induced neuro-plasticity encompasses the entire spectrum of adaptive changes following injuries or diseases of the nervous system demonstrating that the spinal cord is not hard wired after all. These changes are generally viewed as the mechanism behind the limited functional recovery that can be found in animal models as well as in humans with damage to the nervous system. Following spinal cord injury for example, adaptations have been described at the level of the brain, brain stem, and in the spinal cord rostral and caudal to an injury. These adaptations include sprouting of spared fibers, as described by Mebes and Zheng, but also involve sprouting of lesioned fibers, changes in cellular properties, and likely changes at other physiological levels (e.g., synapses). Additional results that prompted the shift towards promoting plasticity came from findings that treatments originally intended to promote regenerative growth notably promoted sprouting of spared and injured nerve cells (Raineteau et al., 2001; Garcia-Alias et al., 2009). This general trend in the field of SCI raises various questions. First of all, one wonders whether this shift indicates that research on regeneration has lost momentum or whether it has left the limelight because of the generally under whelming success in the laboratory and of clinical trials. This impression, although not necessarily accurate, may be the result of a number of factors. First of all, as soon as a treatment enters clinical trials, results can only be produced at a much slower pace, and mostly speculations surface. Secondly, in most cases clinical trials only address one component involved in the poor regenerative ability of central nervous system neurons. Consequently, initial results of a single treatment might appear disappointing although it is widely accepted that a meaningful treatment for spinal cord injury will not consist of a "magic bullet", but a combination of approaches. Furthermore, it has now generally been acknowledged that long distance regeneration is not really necessary for functional recovery. In fact, neurons can actually form "detour" pathways, for example by connecting onto spared neurons (Fouad et al., 2001; Vavrek et al., 2006). Lastly, another recent development away from the focus on extrinsic growth inhibitors (in the CNS environment) towards intrinsic mechanisms that inhibit regenerative growth of injured nerve cells has been promoted by studies in which the PTEN pathway has been modified (Park et al., 2008), and the stunning findings of the abilities of embryonic stem cell grafts when transplanted into the spinal cord of adult rats (Lu et al., 2012).

Another question is about the prospects of plasticity as a treatment target and its possible impact on recovery. To answer this question is extremely difficult as the magnitude of plasticity dependent functional recovery is likely affected by a multitude of factors, lesion severity being the most prominent. For example, the spontaneous recovery following a severe spinal cord injury is very limited to non-existent. Furthermore, plasticity induced recovery is also likely based on a multitude of adaptive changes (i.e., compensation) in neuronal networks and motor behaviors. It is also very unlikely that we will be able to really interpret the entity of these complex changes, as our understanding of neuronal networks even in the uninjured CNS is still rather limited. Furthermore, focusing solely on plasticity research may quickly reach its limitation. For example, plasticity is limited by the amount of spared tissue, and rehabilitative training, currently the best established plasticity-promoting treatment, has been shown to promote surprising recovery, but this recovery is often based on compensation. In other words, plasticity-promoting treatments can neither restore tissue damage nor restore motor function to pre-injury performance, but it may facilitate the efficient use of remaining CNS tissue. Lastly, it should not be forgotten that plasticity is also involved in detrimental effects including neuropathic pain, spasticity and autonomic dysreflexia.

In conclusion, the field of spinal cord injury has seen many trends over the last years, some of them have lost momentum, others seem to have been abandoned, and as a result of this limited success new approaches are quickly seen as a salvation. At the end, however, most agree that spinal cord injury will require a well-balanced treatment approach. This will include neuro-protective efforts, regeneration promoting treatments that will go hand in hand with plasticity promoting treatments, and last but not least rehabilitative training to translate plasticity into actual recovery.

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