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·**Editorial**·

An update on spinal cord injury research

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Spinal cord injury (SCI) is an ever-increasing challenge. Severe injury can cause long-term loss of sensory and motor functions, as well as other chronic conditions, such as neuropathic pain and autonomic dysreflexia. So far, most research has been focused on acute injury. However, due to the lack of treatment, more and more individuals with this condition enter a chronic state, to which very little research effort has been dedicated.

SCI is a complex condition. It involves damage to axons, death of neurons, neuroinflammation, glial scar formation, loss of myelin, and lack of remyelination. It is clear that effective treatment will require combinatorial approaches. The 12 invited articles for this special issue on SCI provide an update on many of these areas of SCI research. Here, I highlight the articles and reviews by theme.

Severe SCI involves severing of axons, breaking ascending and descending connections. Inhibitory molecules in the environment of the adult central nervous system, such as the myelin-associated inhibitors and proteoglycans in glial scars, were thought to be the major cause of the lack of regeneration for many years[1]. However, efforts to regenerate axons across a lesion site in the mammalian spinal cord by overcoming this inhibition have not been successful. In some cases, axon regeneration into cell grafts can be achieved, as in studies using preconditioning lesion paradigms of sensory axons[2]. But few axons project beyond the lesion and reach long-range targets. In recent years, more attention has been shifted to enhancing the intrinsic growth capacity of adult central nervous system axons. Deletion of pTEN (phosphatase and tensin homolog) induces unprecedented regeneration across the fully-transacted spinal cord[3]. Neurons derived from embryos or induced pluripotent stem cells that have strong intrinsic growth properties can ignore inhibitory cues in the adult spinal cord and grow long distances up and down the cord[4]. In partial injury, rerouting and sprouting of axons result in circuit reorganization in the spared tissue and have been shown to be effective in restoring function using a combination of pharmacological and electrophysiological stimulation and robot-assisted rehabilitation techniques[5,6].

Molecular mechanisms that promote or inhibit axon growth have been studied, using various injury paradigms, in different neuronal types and species. Some species have poor central regeneration, whereas others have the capacity to regenerate. Axons in the peripheral nervous system of mammals also show extensive regeneration. The review by Martin Oudega of the University of Pittsburgh[7] provides a comprehensive discussion comparing the molecular mechanisms found in mammals and zebrafish. These comparisons allow for a better understanding of the underlying principles. Remarkably, regeneration in the zebrafish central nervous system is also incomplete. Some axon tracts can regenerate but others cannot. This makes zebrafish an interesting model system for SCI research along with the traditional mammalian models such as rats and mice. Feng-Quan Zhou of Johns Hopkins Medical School[8] discusses signaling mechanisms that lead to axon regeneration in the mammalian peripheral nervous system, in *Drosophila* and in *Caenorhabditis elegans*. Jeff Twiss of the University of South Carolina[9] contributes an original paper reporting that protein translation machinery is present in the peripheral branches of the axons of mammalian dorsal root ganglion cells, which can regenerate, suggesting that the capacity of local protein thesis is essential for regeneration.

The glial scar presents strong inhibitory cues for

regeneration, an influence yet to be overcome. At the same time, the glial scar provides a barrier against inflammation to limit secondary injury, and this is beneficial[10,11]. Cheng He of the Second Military Medical University (Shanghai)[12] discusses the complex role of the glial scar in influencing axon regeneration and neuroinflammation. The choice of appropriate experimental systems and species for SCI research is crucial. Jae Lee of the University of Miami[13] provides a comprehensive discussion of different experimental systems for SCI, animal species, and lesion paradigms.

Injury can cause neuronal loss. So keeping neurons alive is of high priority. Gong Ju of the Fourth Military Medical University (Xi'an)[14] contributes an original research article on the role of Batroxobin in protecting neurons, which may have therapeutic potential. Qiang Liu of the First Clinical Medical College of Shanxi Medical University (Taiyuan)[15] reports that valproate reduces autophagy and promotes neuroprotection.

Improvement of locomotor function has been attributed to axons that regenerate across the lesion site. Wutian Wu of the University of Hong Kong[16] contributes an original research article showing that sometimes such functional improvement may be unrelated to the regeneration of these particular axons. He proposes that adaptation of neural circuits in the spinal cord below the transection site may contribute to improved function, suggesting that the circuitry in the spared tissue has adaptive potential that has not been adequately appreciated.

Jean-Marie Cabelguen of the University of Bordeaux[17] summarizes insights from studies of lower vertebrates that have extensive capacity for regeneration and functional recovery in the central nervous system. However, even in the salamander, regeneration is imperfect. The number of axons achieving correct innervation is less than normal and regenerated axons can innervate inappropriate targets in transected animals. Interestingly, neither new brainstem neurons (neurogenesis) nor axon collaterals from unlesioned neurons (sprouting) contribute to the restoration of descending projections after spinal cord transection in salamanders, fish, and larval lampreys. This suggests that plasticity is limited. In turtles, even when regeneration of axons does occur, functional recovery is incomplete (limited to stepping). This suggests that even if we achieve massive regeneration of central nervous system axons in mammals, we may still face the issues of the extent of regrowth and correct targeting for functional recovery, which require a better understanding of the mechanisms of axon growth and guidance. In the completely transected fish and cat, daily training can result in functional recovery, suggesting that sensory afferents play crucial roles in reactivating the locomotor central pattern generator. This is potentially consistent with the findings reported by Wutian Wu[16] in this issue.

Studies in some areas of SCI research have entered the phase of therapeutic development. James Fawcett of the University of Cambridge[18] summarizes work centered around combinatorial treatment with Chondrotinase ABC and other approaches to achieve regeneration based on progress in molecular signaling in glial scar inhibition. Riyi Shi of Purdue University[19] discusses an interesting tissue-engineering approach using polyethylene glycol, which reseals membrane and repairs mitochondria to reduce oxidative stress and minimize secondary injury. Agnes Haggerty of the University of Pittsburgh[20] covers promising biomaterials for the repair of damaged spinal cord. These exciting efforts will help accelerate translational research in SCI.

The success of SCI repair depends on multidisciplinary approaches that address multiple aspects of injury responses. More robust axon regeneration with proper guidance and synapse specificity are the ultimate goals for restoring maximal function. This will probably most effectively be done in combination with functional rehabilitation. Effective neuroprotective agents will enhance success in the long-term and should be included in the care package. Better understanding of the neural circuit functions controlling sensory-motor behaviors will provide more sophisticated molecular and rehabilitation designs. Using proper animal models for preclinical studies will also help identify promising therapies. A more severe and rapidly growing condition, traumatic brain injury, poses ever-increasing challenges. Even less is known about traumatic brain injury. It is conceivable that these two areas of research will have more and more interactions in the future.

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