



Tune the cord into right chords—activating a “paralyzed” immune system by silencing thoracic interneuron

Ruyi Huang, Daniel C. Lu

Neurosurgery Department, University of California, Los Angeles, USA

Correspondence to: Ruyi Huang, Neurosurgery Department, University of California, Los Angeles, USA. Email: rebecca1ruyi@gmail.com; Daniel C. Lu, Neurosurgery Department, University of California, Los Angeles, USA. Email: DClu@mednet.ucla.edu.

Provenance: This is a Guest Editorial commissioned by Section Editor Ziwei Li (Department of Molecular, Cell & Developmental Biology, University of California, Los Angeles, USA).

Comment on: Ueno M, Ueno-Nakamura Y, Niehaus J, *et al.* Silencing spinal interneurons inhibits immune suppressive autonomic reflexes caused by spinal cord injury. *Nat Neurosci* 2016;19:784-7.

Received: 11 May 2017; Accepted: 23 May 2017; Published: 30 August 2017.

doi: 10.21037/amj.2017.06.07

View this article at: <http://dx.doi.org/10.21037/amj.2017.06.07>

Spinal cord injury (SCI) results in devastating impairment of motor function. An under-appreciated yet equally important complication in chronic SCI is infection. The increased risk of infection in patients living with SCI has traditionally been attributed to motor-paralysis such as dysphagia or neurogenic bladder resulting in pneumonia or urinary tract infection. However, a condition known as SCI-induced immune depression syndrome is thought to decrease adaptive and innate immunity, leading to increased susceptibility to infections (1). A study by Ueno *et al.*, seeks to elucidate the cellular mechanism of this phenomenon (2).

Immunologically, SCI is thought to be a condition associated with immune suppression and concomitant state of chronic inflammation (3). The immune system is under neurological control via the direct innervation of primary and secondary lymphoid tissues by autonomic nerve fibers of the sympathetic nervous system (4). As lymphoid organs such as the spleen are innervated by sympathetic neurons that originate from regions throughout the thoracolumbar spinal cord, an injury at or above this spinal cord level may induce immune suppression (5). Segmental spinal cord level-dependent impairment in B-cell function has been demonstrated in mice when comparing high (T3) to mid-thoracic (T9) SCI. It has been shown that after high thoracic SCI, autonomic control of the spleen was disrupted that led to immune suppression, whereas mid-thoracic

SCI preserved autonomic control of the spleen resulting in intact B-cell activation response (6).

Similar results were observed by Ueno *et al.* in that splenic atrophy and leucopenia were observed in high (T3) but not mid-thoracic (T9) SCI. The authors compared the spinal cord-spleen circuit in high (T3) and mid-thoracic (T9) SCI by injecting GFP-expressing pseudorabies virus (PRV) into spleen. The following two aspects were compared between T3 and T9 SCI:

- (I) The spatial distribution of the spleen-innervating neurons in the gray matter of thoracic spinal cord, and;
- (II) The number of interneurons that form new synapses with sympathetic preganglionic neurons (SPNs) after the spinal cord injury.

The results showed that there was a significant increase of the thoracic interneurons forming new synapses with SPNs after T3 SCI while no significant change after T9 SCI.

Neurotransmitter staining results further revealed that these spleen modulating SPN were cholinergic excitatory neurons, whereas the SPN presynaptic interneurons were glutamatergic excitatory neurons. This is the first time that the splenic neuromodulatory SPNs and the associated presynaptic interneurons have been identified, in addition to the distribution of these neurons after SCI.

By comparing the cholinergic SPN and glutamatergic SPN presynaptic interneuron distribution after high (T3)

to the mid-thoracic SCI (T9), the number of interneurons significantly increased after high-thoracic injury but remained the same after mid-thoracic injury (7). This suggests that the loss of innervation from the brain induced neuronal plasticity in high thoracic level while mid-thoracic SCI did not perturb the splenic neural circuit. The increase of the glutamatergic interneurons after high-thoracic SCI also suggests that the splenic immune suppression may be caused by SPN hyper-excitation, a result of increased glutamatergic interneurons. The hyper-excitation of SPN induced splenic norepinephrine elevation and suppressed immune function. This hypothesis was validated by rescue of the immune suppression in high-thoracic SCI through designer receptors exclusively activated by designer drugs (DREADDs)-induced SPN-presynaptic interneuron inhibition.

SCI results in severe functional deficits along with immunological complications. This study provides a better mechanistic understanding of the neural-immune circuit that results from immunosuppression after SCI. Development of inhibitors of these excitatory spinal interneurons through cell-based therapies and pharmacological agents may effectively address this complication in individuals suffering from SCI.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

doi: 10.21037/amj.2017.06.07

Cite this article as: Huang R, Lu DC. Tune the cord into right chords—activating a ‘paralyzed’ immune system by silencing thoracic interneuron. *AME Med J* 2017;2:130.

to declare.

References

1. Kopp MA, Druschel C, Meisel C, et al. The SCIentinel study--prospective multicenter study to define the spinal cord injury-induced immune depression syndrome (SCI-IDS)--study protocol and interim feasibility data. *BMC Neurol* 2013;13:168.
2. Ueno M, Ueno-Nakamura Y, Niehaus J, et al. Silencing spinal interneurons inhibits immune suppressive autonomic reflexes caused by spinal cord injury. *Nat Neurosci* 2016;19:784-7.
3. Held KS, Steward O, Blanc C, et al. Impaired immune responses following spinal cord injury lead to reduced ability to control viral infection. *Exp Neurol* 2010;226:242-53.
4. Allison DJ, Ditor DS. Immune dysfunction and chronic inflammation following spinal cord injury. *Spinal Cord* 2015;53:14-8.
5. Lucin KM, Sanders VM, Jones TB, et al. Impaired antibody synthesis after spinal cord injury is level dependent and is due to sympathetic nervous system dysregulation. *Exp Neurol* 2007;207:75-84.
6. Cruse JM, Lewis RE, Bishop GR, et al. Neuroendocrine-immune interactions associated with loss and restoration of immune system function in spinal cord injury and stroke patients. *Immunol Res* 1992;11:104-16.
7. Ankeny DP, Lucin KM, Sanders VM, et al. Spinal cord injury triggers systemic autoimmunity: evidence for chronic B lymphocyte activation and lupus-like autoantibody synthesis. *J Neurochem* 2006;99:1073-87.