Enhancing axon regeneration and neuroplasticity after spinal cord injury:

Bridging the gap between development and disease

ABSTRACT

The precise wiring of the adult mammalian central nervous system (CNS) is determined during axon growth, guidance and neuroplasticity during and shortly after development. This intricate system is unable to regenerate when the adult spinal cord is injured. It's not well understood how to translate what is known about developmental processes into therapies for spinal cord injury (SCI). Therefore, effective therapies are difficult to find. This thesis aims to fill an important gap in our understanding of how developmental strategies for axonal growth and plasticity are exploited in SCI regeneration. In particular, we will contrast two approaches: (i) reducing the inhibitory environment that forms around the lesion, and (ii) exploiting the inhibitory environment for regeneration by forcing the overexpression of an appropriate integrin isoform in sensory neurons and allowing axons to grow on this environment. In this thesis, Aim 1, we used 4-methylumbelliferone (4-MU) to reduce the inhibitory environment formed around the lesion. The first step was to assess the potential adverse effects of long-term treatment. Using immunohistochemistry, proteomics, biomechanics, qPCR, behavioural tests and commercially available blood and urine tests, we found no irreversible adverse effects. Our next step was to test whether 4-MU could play a role in chronic SCI. 4-MU treatment reduced scarring after chronic SCI. However, the current dose was not sufficient to suppress SCI-induced CS-GAG upregulation. Further dose adjustment will be required to improve functional recovery after SCI. In Aim 2 of this thesis, the integrin adhesion molecule together with its activator was expressed in sensory neurons using a viral vector. The sensory pathway was partially restored in the presence of this adhesion molecule. Many axons regenerated from the thoracic lesion to the brainstem. This is a distance of 4-5 cm. Taken together, these findings have implications for our understanding of the developmental mechanisms of spinal cord regeneration.

Key words

4-methylumbeliferone, extracellular matrix, gene therapy, integrin, perineuronal nets, plasticity, regeneration, spinal cord injury