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Investigating histological changes in spinal neuroplasticity following a novel regulated gene therapy approach for treating spinal cord injury

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Spinal cord injury (SCI) leads to severe functional deficits and poses a significant burden to individuals and the society. Current treatment options are limited and there are no curative therapies. An important pathological consequence of SCI is the 'glial scar'. A sugar molecule found in the extracellular matrix (ECM) is associated with the glial scar, and acts to prevent axonal regeneration. The main inhibitory components of the ECM molecule are sugar sidechains. A bacterial enzyme, chondroitinase ABC (ChABC), degrades the sugar sidechains, thus permitting axonal sprouting and subsequent functional improvement. Previous approaches to attenuate the inhibitory effect of GAG sidechains involved administering ChABC via multiple injections or infusions, but a more optimal delivery mechanism can be achieved via gene therapy. Recent work assessed a novel, temporally-regulated gene delivery system using a lentiviral vector, where administration of doxycycline induces ChABC expression (dox-i-ChABC). Here, we histologically investigate the effects of dox-i-ChABC following clinically-relevant cervical contusion injury in female adult rats, comparing short-term (2.5 weeks) vs. long-term (eight weeks) ChABC expression on sugar sidechain digestion and neuroplasticity. The present study demonstrates extensive sugar sidechain digestion after short- and long-term dox-i-ChABC treatment. Additionally, we establish that only long-term dox-i-ChABC treatment confers increased density of excitatory (glutamatergic) neurotransmitter transporters within spinal grey matter. This increased glutamatergic innervation following SCI is a novel finding which may contribute to improved functional recovery and direct further research within the field.