Attenuation of Robust Glial Scar Formation after Chronic Nerve Compression Injury Can Facilitate Functional Recovery

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Abstract

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Purpose: Early surgical management of chronic nerve compression (CNC) injuries often improves sensation but offers limited reversal of late motor atrophy. Spinal cord injury (SCI) models have shown formation of glial scar composed of chondroitin sulfate proteoglycans (CSPGs), degradation of which leads to improved functional outcomes. We hypothesized that persistent glial scar composed of CSPGs and other extracellular matrix (ECM) molecules such as laminin-a2, fibronectin, and collagen-IV might similarly account for poor motor recovery after decompression in later stages of CNC injury, and that digestion of glial scar would result in improved functional recovery.

Methods: CNC injury was created in C57BL/6 mice and Sprague Dawley rats by placing silastic tubing around the sciatic nerve. Mouse nerves were harvested after 2-weeks and 6-weeks while rat nerves were harvested at 4-months and 6-months. Electrophysiology was performed to confirm CNC injury. Western blot, PCR, and immunohistochemistry (IHC) were performed to determine levels of CSPGs including decorin, aggrecan, brevican, and versican, as well as of other ECM molecules including collagen-IV, fibronectin, and laminin-a2. A subset of mice were treated with either surgical decompression alone, or decompression coupled with intraneural injection of chondroitinase ABC (AMS Biosciences, 0.2 μg/uL) at 6-weeks.

Results: Aggrecan showed the greatest change in mRNA levels following rat CNC with marked bimodal increases of nearly 25-fold at 1 month and 18-fold at 5-months. IHC analysis for mouse collagen IV, laminin a2, and fibronectin showed perineurial scarring

at 2-weeks. This correlated with western blot data in mice at 2-weeks that showed 6-fold upregulation of fibronectin, 1.4-fold upregulation of laminin-a2, and 2-fold upregulation of collagen-IV. IHC and western blot for mouse decorin demonstrated minimal changes to expression in compressed nerves at 2-weeks but marked upregulation of expression by 6-weeks in epineurium and perineurium. Decompression with intraneural injection of chondroitinase ABC at 6-weeks resulted in marked attenuation of decorin expression.

Conclusions:

• These data demonstrate that a progressive and significant upregulation of CSPGs and other ECM components contribute to the pathogenesis of compression neuropathies in murine models, and that different chondroitin sulfate proteoglycans exhibit a temporally-dependent expression pattern.

Clinical Relevance:

• CNC injuries such as carpal and cubital tunnel syndromes result in demyelination and glial scar formation that cause patients significant morbidity despite optimal medical and surgical management.

• These data demonstrate that a progressive and significant upregulation of CSPGs and other ECM components contribute to the pathogenesis of compression neuropathies in murine models.

• Analogous to SCI, degradation of persistent scar can result in significant functional recovery. These data therefore present a potential novel therapeutic avenue for treatment of late-stage, irreversible compression neuropathies.