Neuroprotective approaches to enhance recovery in cervical spondylotic myelopathy
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Although cervical spondylotic myelopathy (CSM) is a common cause of chronic spinal cord dysfunction in humans, little is known about the molecular mechanisms underlying the progressive neural degeneration characterized by this condition. To characterize and validate potential neuroprotective strategies, we developed novel mouse (twy/twy) and rat models of chronic progressive cervical spinal cord compression to show a significant decline in locomotor function, forelimb function, trunk stability/coordination, an increase in mechanical allodynia, and impaired axonal conduction. Based on animal models of CSM, we hypothesized that Fas-mediated apoptosis and inflammation may play an important role in the pathobiology of human CSM and that neutralization of the Fas ligand (FasL) using a function-blocking-antibody would reduce cell death, attenuate inflammation, promote axonal repair and enhance functional neurological outcomes in rodent models of CSM. We examined molecular changes in post-mortem human spinal cord tissue from eight cases of patients with CSM and four control cases using immunohistochemistry. Complementary studies were conducted using 4 month-old twy/twy mice treated with a FasL specific antibody (50ug i.p twice weekly for 4 weeks; n=12 per group). We found Fas-mediated apoptosis of neurons and oligodendrocytes and an increase in inflammatory cells in the compressed spinal cords of patients with CSM. Furthermore, neutralization of the Fas ligand with a function-blocking antibody in twy/twy mice reduced macrophage/microglia infiltration, glial scar formation and caspase-9 activation, and upregulated Bcl-2 expression, resulting in functional neurological recovery. Our data demonstrate, for the first time in humans, the potential contribution of Fas-mediated cell death and inflammation to the pathobiology of CSM. The targeting of a death receptor pathway is a viable neuroprotective strategy to attenuate neural degeneration and optimize neurological recovery in CSM. Our findings will open the door to the possibility of complementary treatments to surgical decompression.