Characterization of TDP-43 delta NLS mice: behavior and biomarker analyses

AUTHOR BLOCK: *H. B. FERNANDES, I. MORGANSTERN, J. BELTRAN, M. KWAN, J. SHEA, A. GHAVAMI, D. HAVAS, T. HANANIA; Psychogenics Inc., Psychogenics, Paramus, NJ

Abstract:
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive loss of upper and lower motor neurons producing muscle denervation, motor impairments and brain atrophy. Deposition of insoluble cytosolic inclusions of TAR-DNA binding protein (TDP-43) correlates with ALS-related pathology in affected tissues. To study the progression of ALS phenotypes and establish a model for testing therapeutic interventions, we characterized TDP-43ΔNLS mice (Walker et al, 2015). These inducible rNLS8 mice were generated by crossing transgenic mice expressing tTA under the control of the human neurofilament heavy chain (NEFH) promoter with tetO-hTDP-43ΔNLS mice containing a defective nuclear localization motif (ΔNLS). Administration of Dox suppresses expression of total and phosphorylated forms of hTDP-43ΔNLS, rescuing the disease phenotype. TDP-43ΔNLS mice showed dramatic loss of body weight following Dox cessation, increased tremors and hindlimb clasping, impaired gait and muscle strength and decreased survival compared to tTA control mice. EMG assessment of muscle function 4 weeks after DOX removal showed an increase in the latency of muscular contraction and decreased response amplitudes of muscle contractions following motor nerve stimulation in TDP-43ΔNLS animals, impairments whose increasing severity correlated with the amount of time spent off Dox. Histological analysis revealed strong overexpression of TDP43 in perinuclear cytoplasmic inclusions along with deposition of pTDP43 aggregates in multiple brain regions including hippocampus, cerebral cortex, dorsal striatum and cerebellum. This model recapitulates deregulated translocation of TDP43 from nucleus to the cytoplasm, a major pathology seen in ALS patients.TDP-43 pathologies were accompanied by increased expression of inflammatory marker transcripts in cortex, astrogliosis, and microglial activation in affected brain regions. Similar pathologies were detected in spinal cord but at lower level of severity than in the brain. Dramatic elevations in neurofilament light chain, a biomarker of neurodegeneration, were seen in plasma and CSF of TDP-43ΔNLS animals at 10 weeks of age, 5 weeks after Dox withdrawal. In summary, expression of human TDP-43ΔNLS in this mouse model of ALS resulted in the development of cytoplasmic inclusions in multiple brain regions and spinal cord, a loss of murine nuclear TDP-43, progressive loss of muscle strength and function, and motor impairments leading to death. These impairments were observed in both genders. This mouse model of ALS provides a rapid progressive phenotype for testing novel therapeutic strategies.