DISORDERS OF THE NERVOUS SYSTEM

Assessing degeneration of corticospinal tracts in a TDP-43 transgenic mouse model of ALS/FTD: application of 3D reconstruction in cleared tissue.

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The neurodegenerative diseases amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) represent two ends of one spectrum disorder, termed ALS/FTD. These incurable pathologies are now classified as “TDP-43 proteinopathies”, since mislocalization and aggregation of the nuclear protein TDP-43 are hallmark features of most cases. A main feature of ALS/FTD is degeneration of the corticospinal tract (CST), composed of axons of upper motor neurons, being the main motor pathway involved in voluntary movement. We are using a novel approach, combining a cost-effective unsectioned brain/spinal cord clearing technique, fluoroRuby staining, one-photon confocal microscopy and 3D reconstruction to study the morphological changes in the CST of TDP-43 transgenic (TG) mice. We have previously shown in mice that inducible overexpression of a cytoplasmic (ΔNLS) form of TDP-43 in forebrain neurons evokes neuropathological and behavioural changes that recapitulate several features of TDP-43 proteinopathies. Our preliminary results showed proper and consistent tracer delivery, with similar number of labelled cortical neurons in control and TG mice. TDP-43-ΔNLS expression decreased the length of cortical apical processes and the number of cervical axons. Remarkably, suppression of TG expression (displaying reversible motor phenotypes) led to an increase in cervical axonal branching. These studies will help to elucidate the mechanisms underlying the motor phenotypes in ALS/FTD.