A postsynaptic pathway of TDP-43-mediated pathology in ALS

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Dendritic spines are highly dynamic postsynaptic structures, and their morphology reflects the stability, maturity and strength of synaptic connections. The turnover and stabilisation of dendritic spine types underlies neuronal plasticity; a phenomenon describing the molecular bases of learning and memory, mediated by synaptic networks. In Amyotrophic Lateral Sclerosis, synaptic dysfunction has been increasingly implicated in disease onset and progression of- however, why the motor cortex is particularly susceptible to the mechanisms driving network dysregulation is still unknown. We have found that TDP-43, the primary protein component cytoplasmic aggregates in ALS, is involved in maintaining neuronal synapses in mouse models of ALS - regulating the number and maturation of dendritic spines. Spine changes occur well before symptom onset in the motor cortex; but not the somatosensory cortex, indicating that this is one of the earliest pathological changes associated with misprocessed TDP-43. We have advanced these finding through the application of 2-photon live imaging to reveal that the turnover rates of dendritic is compromised in the presence of mutant TDP-43. The pathological influence of TDP-43 misprocessing at the spine may be due to its role in activity-dependent RNA translation, crucial for the viability of postsynaptic structures. Here, we have identified that mutant TDP-43 drives increased cytoplasmic protein expression and causes alterations in the composition and localisation of AMPA receptor proteins specifically at the spine head. Further, the motor cortex may be specifically vulnerable to TDP-43-mediated dendritic spine deficits. The outcomes of this study identify mechanisms that may drive ALS, and also provide a greater understanding of the vulnerability of the motor cortex, informing therapeutic development and subsequent clinical trial design for all future therapeutic interventions.