Loss of TDP43 in Motor Neurons Leads to Deficits in Axonal RNAs in an Animal Model of ALS

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Amyotrophic Lateral Sclerosis (ALS) is a lethal neurodegenerative disease that affects both the upper and lower motor neurons of the CNS. Mutations in TDP-43, a putative RNA binding protein, exhibit pathological hallmarks of familial ALS. We hypothesize that the loss of TDP-43 in ALS leads to the reduction in the localization of RNAs into the motor neuron axons and that this loss contributes to the axonal degeneration seen in ALS. Here, we have developed a unique microfluidic based system to isolate axonal RNA from motor neurons to identify the RNAs that are absent when TDP-43 is lost. Using siRNA-based knockdown of TDP-43 in our microfluidic culture system, we have identified several axonal RNAs that are reduced when TDP-43 protein levels are decreased. , Deep sequencing of the axonal RNA populations in motor neurons from control and TDP-43 knockdown cultures will help to identify the entire pool of lost RNAs. Based on these studies, we will determine whether these RNAs directly interact with TDP-43 using an immunoprecipitation method that we have optimized to detect direct RNA-RNA binding protein interactions.

Awards Won:

Third Award of $1,000