“RNA-Binding Proteins in Amyotrophic Lateral Sclerosis: Models and Mechanisms”

Abstract:

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, is a fatal, late onset, neurodegenerative disease for which there are currently no effective therapies. ALS is the most common form of Motor Neuron Disease, and is characterized by the loss of both upper and lower motor neurons. Death typically occurs within 3-5 years after diagnosis, and is most commonly due to respiratory failure. Recently, mutations in genes that code for RNA-binding proteins have been linked to ALS pathology, suggesting that perturbation of RNA metabolism may be the cause of disease onset. Mutations of the gene Fused in Sarcoma (FUS), which codes for the protein FUS, have been linked to both familial and sporadic forms of ALS. FUS is a DNA/RNA-binding protein that plays critical roles in RNA metabolism including RNA trafficking and alternative splicing. Using a Drosophila melanogaster model for FUS-associated ALS that was previously developed by our laboratory, we performed an unbiased genetic screen to identify modifiers of ALS-associated phenotypes. One gene identified in this screen, muscleblind (Mbl), is the Drosophila homolog of human muscleblind-like (MBNL). MBNL is also an RNA-binding protein involved in alternative splicing, and has previously been linked to Myotonic Dystrophy in humans. We have begun characterizing the nature of the interaction between FUS and Mbl, in order to better understand the link between these two proteins in neurodegeneration. The results of this work will not only help us to better understand FUS-associated ALS pathogenesis, but will also provide insights into the role of MBNL in Myotonic Dystrophy, and will therefore have broader implications for neurodegeneration as a whole.