WRIGHT STATE UNIVERSITY | BIOMEDICAL SCIENCES PhD PROGRAM

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DISSERTATION DEFENSE

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PhD Candidate

"Rescue of ALS Protein FUS Toxicity by TAF15"

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9:00 a.m.

NEC Auditorium (room 101)

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Hayden, Elliott, Biomedical Sciences PhD Program
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Amyotrophic Lateral Scleroses (ALS) is a neurodegenerative disease characterized by the degeneration of upper and lower motor neurons in the brain and spinal cord leading to progressive paralysis and ultimately death within 5 years of symptom onset. Only two drugs are approved by the Food and Drug Administration (FDA) for treating ALS that slow the disease progression by about 3 months.

Mutations in the gene Fused in Sarcoma (FUS) cause inherited forms of ALS. FUS is a nuclear, multifunctional RNA-binding protein (RBP) involved in multiple RNA metabolic pathways. Mutations in FUS cause mislocalization of the protein from the nucleus to cytoplasm, where it forms inclusions that colocalize with stress granules. Over-expression of human FUS in the budding yeast, *Saccharomyces cerevisiae,* results in cellular toxicity, cytoplasmic aggregation and localization to stress granules, recapitulating phenotypes of mutant FUS in mammalian models and patients. In recent years, perturbations in RNA metabolism and RNA binding proteins has emerged as an underlying defect in ALS pathogenesis. FUS is one of the first RBPs linked to ALS, and modeling FUS toxicity in yeast will enhance our understanding of how RBPs contribute to neuronal toxicity in ALS.

Using a yeast model of FUS toxicity, we designed and completed a genetic screen to identify human genes that suppress FUS induced toxicity. Enrichment analysis of the suppressor genes showed an over representation of genes with RNA binding function and ribonucleoprotein complex localization. A subset of the suppressors physically interact with FUS and colocalize with FUS aggregates. We focused on the FUS suppressor TATA-Box Binding Protein Associated Factor 15 (TAF15) for further study since TAF15 has been found in a complex with FUS and has a similar function and structure to FUS.

We tested TAF15 against three other toxic neurodegenerative disease proteins; TAF15 suppressed toxicity of FUS and not the others. TAF15 did not reduce FUS protein expression or re-localize FUS from cytoplasmic foci to the nucleus. TAF15 and FUS interact with each other and colocalize with p-bodies and stress granules. The C-terminus of TAF15 is essential for its interaction with FUS. Deletion of TAF15 C-terminus eliminates its interaction with FUS and its ability to suppress toxicity, indicating that rescue is mediated through the interaction. TAF15's RNA recognition motif (RRM) is critical for rescue since mutation of phenylalanine residues within the RRM eliminates rescue. Wild type (WT) TAF15 but not TAF15 with a mutated RRM reduced the number of FUS aggregates. This indicates that TAF15, through its RNA binding ability, is able to reduce FUS aggregates and therefore, stress granules. This study establishes that TAF15, an interacting partner of FUS, can suppress FUS toxicity without decreasing FUS protein levels or altering cytoplasmic localization. As the suppressive effect of TAF15 is associated with reduction in the number of FUS stress granule, disassembling pathological stress granules may represent a therapeutic target.