# Molecular Basis of TDP-43 Proteinopathies: Disease Models and Mechanisms

https://neurodegenerationresearch.eu/survey/molecular-basis-of-tdp-43-proteinopathies-disease-models-and-mechanisms/

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**Research Abstract**

DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is a devastating adult-onset neurodegenerative disease that wreaks havoc on motor neurons. A progressive and fatal muscle paralysis ensues, causing death within 2 to 5 years. Recently, a central role for RNA binding proteins and RNA metabolism pathways has emerged. The protein TDP-43 was recently identified as the major disease protein in pathological inclusions in both ALS and frontal temporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U). Moreover, mutations in

the TDP-43 gene have now been identified in sporadic and familial ALS patients. Pathology and genetics both converge on TDP-43 being central to the pathogenesis of these diseases. In the first five years of this research project, we have generated in vitro and in vivo TDP-43 proteinopathy models to explore TDP-43. We have harnessed the simple yeast model system to study TDP-43's properties and the effect of ALS-linked mutations. Our preliminary data demonstrate: 1) a critical role for the RNA recognition motif and carboxy-terminal region of TDP-43 in mediating aggregation and cellular toxicity, 2) increased aggregation and toxicity caused by a disease-linked TDP-43 mutation, and 3) genetic screens identified multiple RNA binding proteins as potent toxicity modifiers. One of these, Pbp1, is the yeast homolog of human ataxin 2 and we identified polyglutamine expansions in ataxin 2 as a major genetic risk factor for ALS in humans. We also discovered that deletion of the Dbr1 gene potently suppresses TDP-43 toxicity. The identification of a major genetic risk factor for ALS in humans and a novel and unexpected therapeutic target for ALS starting from the simple yeast model, illustrates the power of this approach. We have also pursued studies beyond TDP-43, focusing on additional RNA-binding proteins, such as FUS, TAF15, EWSR1, and several more. We have discovered a prion-like domain in TDP-43 and FUS and have used this domain to link additional RNA-binding proteins to a class of proteins with similar structural and functional properties. For the next fiv years of this project, with the goal to define TDP-43 disease mechanisms from multiple angles we propose three Specific Aims: 1) Continuing to characterize hits from our yeast TDP-43 toxicity modifier screens to elucidate additional mechanisms of TDP- 43 toxicity and to perform an additional yeast screen of ~1,000 essential genes; 2) Defining the mechanism by which Dbr1 inhibition suppresses TDP-43 toxicity and extending these studies to mammalian cells and animal models; 3) Testing the hypothesis that aggregation-prone RNA-binding proteins contribute broadly to ALS using next generation sequencing approaches.

**Further information available at:**

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