Stress Granules and the Biology of TDP-43

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Stress Granules and the Biology of TDP-43

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Research Abstract

TDP-43 is the principle component of inclusions in amyotrophic lateral sclerosis (ALS) and in some frontotemporal dementia (FTLD-U). TDP-43 is a nuclear RNA binding protein, which translocates to the cytoplasm during stress where it forms cytoplasmic granules. Our research indicates that these cytoplasmic TDP-43 inclusions co-localize with RNA granules termed “”stress granules”” (SGs) in cell models and in the human brain. Disease-linked mutations in

TDP-43 also increase formation of inclusions associated with SGs. These data point to a strong biological connection between SGs and TDP-43. This proposal will address the role of SG-dependent and independent processes in the pathophysiology of ALS. We hypothesize that SG biology stimulates formation of TDP-43 inclusions, and that pathogenic factors linked to ALS increase TDP-43 inclusion formation through a process mediated by SG pathways. Aim 1 will use induced pluripotent stem cells (IPSCs, generated from control and TDP-43 mutant human cell lines) and hippocampal neurons to characterize the regulation of TDP-43 inclusion formation. We will use imaging to determine how disease-linked mutations in TDP-43 modify formation and dispersion of RNA granules under basal or stressed conditions, including genotoxic stress (e.g., effects of ataxin-2 ± expanded polyglutamine regions), excitatory stress (K+) or growth factor stimulation. In each case we evaluate the role of RPCs (including SGs) in particular locations, such as the soma or dendritic arbor, by genetically restricting RPC formation to the nucleus, soma or soma/dendrite, and examining toxicity. Neurodegeneration will be monitored by measuring dendritic length under the different conditions, and putative changes in dendritic structure will be validated in human tissues. In Aim 2 we will identify molecular factors associated with TDP-43 inclusions. We will determine how pathological mutations in TDP-43 or other SG associated proteins modify the proteins and mRNA that associate with TDP-43 under conditions ± inclusions. In Aim 3 we will determine whether TDP-43 forms inclusion through a SG-augmented mechanism in vivo. This aim will apply the work of Aims 1 & 2 to the in vivo setting, using transgenic mice expressing WT TDP-43. We will identify proteins associated with inclusions in inducible TDP-43 WT transgenic mice. We will investigate examine transgenic mouse lines expressing mutant TDP-43 to determine whether expression of ataxin-2 Q21, 31 or 58 increases TDP-43 motor dysfunction, pathology. Finally we will determine whether ataxin-2 knockout inhibits TDP-43 pathology. Investigating the particular elements of the SG pathway that regulate TDP-43 inclusion formation will identify selective approaches for therapeutic intervention to delay or halt the progression of ALS.

Lay Summary

TDP-43 is a RNA binding protein that associates with RNA inclusions, termed stress granules. This proposal will focus on RNA protein complexes and the stress granule pathway to identify molecular factors associated with TDP-43 inclusions and determine how these factors regulate neurodegeneration related to TDP-43.

Further information available at:

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