TDP-43 Proteinopathy in ALS-FTD: Mechanism, Target Validation and Biomarker

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USA

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TDP-43 Proteinopathy in ALS-FTD: Mechanism, Target Validation and Biomarker

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Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic Lateral Sclerosis (ALS), a fatal adult onset motor neuron disease characterized by selective loss of upper and lower motor neurons,

and Fronto-Temporal Dementia (FTD), a common form of dementia characterized by a progressive deterioration in behavior, personality and/or language, share a common disease spectrum. The neuropathology involving Transactivation response element DNA-binding protein 43 (TDP-43) occurs in nearly all cases of ALS and large proportion of FTD, neurodegenerative diseases currently without effective therapy. The overall goals of this proposal are to clarify disease mechanism, validate a novel therapeutic strategy, and develop biomarkers for ALS-FTD. Our recent discovery established that TDP-43, a protein thought to be central in the pathogenesis of ALS-FTD, is a splicing suppressor of non-conserved cryptic exons and that loss of such function leads to down-regulation of a set of mRNA critical for cellular function via nonsense-mediated decay. Supporting the hypothesis that TDP-43 proteinopathy reflects a loss of TDP-43 function, we showed that in brains of ALS-FTD exhibiting TDP-43 proteinopathy, suppression of cryptic exon is impaired. We hypothesize that there exists neuron-specific TDP-43 dependent cryptic exons that would be relevant towards clarifying disease mechanisms to account for the selective vulnerability of neurons in ALS- FTD. We will address this critical question by identifying neuron specific cryptic exons in human neurons lacking TDP-43. We will then confirm whether suppression of such cryptic exons is also compromised in brains of cases of ALS-FTD. We further hypothesize that a specific set of cryptic exons predispose motor or frontal cortex in ALS or FTD cases. To test this possibility, we will determine whether a unique set of cryptic exons is linked either to cases of ALS or FTD. Importantly, we demonstrated in a cell model lacking Tdp-43 that these cryptic exons can be suppressed and cell death prevented by forced expression of a hybrid protein comprised of the N-terminal domain of TDP-43 fused to the splicing repressor domain of a well-characterized suppressor. Our findings offer a novel therapeutic strategy to suppress splicing of cryptic exons using this hybrid protein in an effort t ameliorate neurodegeneration in ALS-FTD. We propose to perform a series of preclinical proof-of- principal studies to validate the efficacy of this approach, information that will be critical or translating such a promising therapeutic strategy to the clinic. Biomarkers, particularly pre-symptomatic ones, for patient selection and monitoring of clinical trials remain a critical unmet need. We hypothesize that neoantigens against expressed cryptic exons represent novel biomarkers for ALS and FTD. We will generate monoclonal antisera to novel epitopes corresponding to several cryptic exons and evaluate their potential as pre-symptomatic biomarkers. Together, results from our proposed studies will have important implications for understanding disease mechanism, validating therapeutic strategy and developing functional biomarkers for ALS-FTD.

Lay Summary

PUBLIC HEALTH RELEVANCE: The identification of abnormalities of an RNA binding protein, called TDP-43, occurring in Amyotrophic Lateral Sclerosis (ALS) and Fronto-Temporal Dementia (FTD) provided the opportunity to design therapies to treat this illness, currently without effective treatment. We recently discovered that when TDP-43 is cleared from the nucleus of the nerve cell, its ability to keep certain unwanted coding elements of genes, called cryptic exons, is compromised in brains of patients with ALS or FTD. This new discovery suggests that loss of this TDP-43 plays an important role in causing nerve cell loss in these patients. Based on our new findings, we have designed a set of experiments to further understand the root cause of ALS and FTD, test a therapy designed to slow down nerve cell loss and develop a way to monitor these abnormalities occurring in blood or spinal fluid of patients. If successful, this type of therapy can be tested in the future in patients with ALS and FTD.

Further information available at:

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