Does TDP-43 dysfunction in astrocytes trigger motor neuron degeneration?

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Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig’s disease), is a fatal neurodegenerative disease that kills motor neurons, leading to paralysis and death. Ten percent of ALS cases are familial and ninety percent are sporadic. Genetic studies have identified multiple causes for the familial ALS, including mutations in SOD1, TDP-43, FUS, UBQLN2, c9orf72 and PFN1 genes. Among these mutant genes, TDP-43

is of particular interest because it is involved in the most ALS cases. TDP-43 intracellular aggregation or TDP-43 proteinopathy, is a prominent pathological feature in the majority (>95%) of ALS cases, including all the sporadic and most of the familial cases. TDP-43 is normally a nuclear protein. But in ALS, TDP-43 accumulates and aggregates in the cytoplasm and is depleted from the nuclei of motor neurons and glia. While TDP- 43 aggregation can harm cells through a gain of toxicity, it could also cause a loss of TDP-43 function by depleting the functional TDP-43 from the nuclei and cytoplasm. TDP-43 maintains its expression level constant by an auto-regulatory mechanism. Perturbation of the level of TDP-43, either by increasing or by decreasing TDP-43 in animal models leads to neurodegeneration and ALS phenotypes. The evidence supports the concept that TDP-43 dysregulation and the consequent TDP-43 dysfunction is a critical driver of neurodegeneration. In recent years, mounting evidence supports the notion that glia play a major role in neurodegeneration. In ALS, most studies have been conducted in models that express mutant SOD1. Investigation on models associated with TDP-43 expression is just beginning and the evidence has been contradictory. Given the potential role of TDP-43 dysfunction in motor neuron degeneration, we have generated a TDP-43 knockdown transgenic mouse model, which has shown the core features of ALS, including age-dependent motor neuron degeneration, muscle weakness and paralysis. An unexpected finding in this mouse model is that TDP-43 was knocked down in astrocytes but the knockdown was undetectable in motor neurons. Based on this result, we hypothesize that TDP-43 dysfunction in astrocytes can drive motor neuron degeneration. We propose to test this hypothesis by generate mice where TDP-43 gene deletion can be induced specifically in astrocytes. By analyzing these mice, we will determine whether a loss of TDP-43 function in astrocytes can cause motor neuron degeneration. The results will shed light on the role of TDP-43 in motor neuron degeneration in ALS.

Further information available at:

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