The pathophysiological role of TDP43 in amyotrophic lateral sclerosis due to C9orf72 mutations

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Research Abstract
Amyotrophic lateral sclerosis (ALS) is a progressive degenerative neurological disorder that predominantly affects the motor system and results in death within 1-5 years of onset. There are no effective treatments. Its pathophysiology is poorly understood and multiple hypotheses exist. There is abundant evidence that RNA splicing is defective in ALS. This is supported by the fact that the signature protein found in the inclusions in ALS, TDP-43, is an RNA binding protein. The most common mutation in ALS patients is a hexanucleotide repeat in the intron of C9orf72, found in 40% of familial and 7% of sporadic cases. Patients with C9orf72 mutations have a characteristic clinical picture and have TDP-43 positive inclusions, such as those found in the majority of ALS patients, but also have atypical TDP43 negative inclusions. The function of C9orf72 as well as its relationship with TDP-43 are still unknown. We will investigate this using the two following hypotheses: Hypothesis 1: Motor neurons with the C9orf72 mutation have different physiology and pathology from sporadic ALS cells and controls. This will be tested using motor neurons derived from iPS cells derived from relevant patients and controls from the ALS clinic. I will analyse survival, TDP43 pathology, neurophysiology and response to cellular stress. Results will be validated using the TDP43 mouse model available in the host laboratory, a C9orf72 mouse model in development and human autopsy findings. Hypothesis 2: The C9orf72 mutation interferes with splicing of mRNA species normally targeted by TDP-43. I will extract RNA from the above cell lines and look for splicing abnormalities using RNA sequencing. I will then create antisense oligonucleotides to silence the mutation and analyse for reversal of the effects identified.

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