TDP-43 and Mitochondrial Dysfunction in ALS

https://neurodegenerationresearch.eu/survey/tdp-43-and-mitochondrial-dysfunction-in-als/

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USA

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TDP-43 and Mitochondrial Dysfunction in ALS

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3

The project/programme is most relevant to:

Motor neurone diseases

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Research Abstract

DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig’s disease, is the most common of the five motor neuron diseases characterized by progressive neurodegeneration of motor neurons in the brain stem and spinal cord. Currently, there is no cure or effective treatment for ALS. The cause of disease is unknown in the majority

of ALS cases. Less than 10% of ALS cases are familial, involving mutations in several genes such as SOD1 and TARDBP. The protein encoded by TARDBP, i.e. TAR DNA-binding protein 43 (TDP-43), was identified as a major component of the histopathological hallmark, i.e., neuronal ubiquitinated inclusions, of degenerating neurons in most forms of ALS and increasing evidence suggests a critical role of TDP-43 in diverse neurodegenerative diseases including ALS and frontotemporal lobar degeneration (FTLD). Unfortunately, how TDP-43 mutant causes neurodegeneration is poorly understood. Interestingly, in our preliminary studies, we also observed significant impairment of mitochondrial bioenergetics in motor neuronal cell lines expressing mutant TDP-43. As mitochondrial dysfunction plays a prominent role in ALS, further more detailed studies should be performed to assess the effect of mutant TDP-43 on mitochondrial function in primary motor neurons in vitro and in vivo, and explore potential underlying mechanisms by which mutant TDP- 43 cause mitochondrial dysfunction. TDP-43 translocates from the nucleus to cytoplasm in of ALS and frontotemporal lobar degeneration (FTLD-U). Unfortunately, few attempt has been taken to investigate its subcellular organelle target(s). Excitingly, our pilot studies found that TDP-43 could be present in the matrix of mitochondria. And, more importantly, TDP-43 interacts with a matrix facing protein critical for mitochondrial electron transport chain, and binds mitochondrial genome encoded mRNA, indicating a direct role of TDP-43 in regulating mitochondrial function. All these exciting finding strongly suggest that TDP-43 may impair mitochondrial function through its specific localization in mitochondria which adversely affects neuronal functions in ALS. Thus, it is important to investigate how TDP-43 is taken up by mitochondria and test whether TDP-43 mitochondrial localization is required for its toxicity on mitochondria and neurons. Our proposed study will be the first systematic and mechanistic study of TDP-43 mitochondrial import as well as TDP-43 induced mitochondrial dysfunction. Our proposed studies will reveal a novel role of TDP-43 in the regulation of mitochondrial function and likely provide novel therapeutic targets for ALS.

Lay Summary

PUBLIC HEALTH RELEVANCE: Mutations in TDP-43 gene cause both familial and sporadic amyotrophic lateral sclerosis (ALS) and TDP-43 pathology is a pathological hallmark of ALS. Although mitochondrial dysfunction is an early and prominent feature in ALS, it is still unclear about the mechanism underlying mitochondrial dysfunction and neurodegeneration in the disease. Our group, for the first time, found the presence of TDP-43 in mitochondria. We propose to perform the detailed investigation of how wild type and mutant TDP-43 are taken up by mitochondria and explore whether and how wild type and mutant TDP-43 in mitochondria is involved in the regulation of mitochondrial and neuronal function. The completion of this project will provide new insights about the pathogenesis of ALS and may lead to novel therapeutic targets for ALS.

Further information available at:

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