Dysregulation of TDP-43 expression in amyotrophic lateral sclerosis and frontotemporal lobar degeneration

https://neurodegenerationresearch.eu/survey/dysregulation-of-tdp-43-expression-in-amyotrophic-lateral-sclerosis-and-frontotemporal-lobar-degeneration/

Principal Investigators

Dr Boris Rogelj

Institution

Zavod BRIS

Contact information of lead PI
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Slovenia

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Dysregulation of TDP-43 expression in amyotrophic lateral sclerosis and frontotemporal lobar degeneration

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Research Abstract

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are two ends of a phenotypic spectrum of disabling, relentlessly progressive and ultimately fatal diseases. There is no cure and until recently we have known very little about their causes. Cytoplasmic TDP-43 positive inclusions are a hallmark of the disease spectrum and can be found in 95% of all ALS and 50% of FTLD cases, which can now be aptly termed TDP-43 proteinopathies. In

order to understand the disease process and look for ways of treatment, discerning pathways that may bring about TDP-43 aggregation is one of the main focuses in the field of ALS and FTLD research. Current
understanding is that changes in de novo synthesis levels, localisation and turnover of TDP-43 may all have a role to play in ALS/FTLD. Cellular and animal model studies have shown that just overexpression of TDP-43 can be pathogenic. We aim to study regulation of TDP-43 expression at the RNA level and involvement of these processes in TDP-43 proteinopathies. The disease importance of RNA related upstream processes has just been further substantiated with association of the GGGGCC expanded repeat in C9orf72 with ALS/FTLD. Using an RNA pull-down method we have shown that TDP-43 3'UTR binds TDP-43 and FUS proteins. In this project we propose to use proteomic approaches to discover other RNA binding proteins (RBPs) that may bind to and regulate TDP-43 mRNA. Using the same method we propose to discover proteins that bind to GGGGCC repeat. We also aim to use phage display of scFvs (single-chain variable fragments of antibodies) to develop a tool for diagnostic analysis of GGGGCC repeats. Cellular stress is another important factor associated with ALS and FTLD. Oxidative stress has been shown to affect transcriptional and translational fidelity leading to increased misincorporation of amino acids. Our preliminary data shows that oxidative stress can affect the isoelectric point of TDP-43 suggestive of amino acid misincorporation. We propose to define the extent and types of
misincorporation in TDP-43. The disease relevance of these findings will be tested on TDP-43 transgenic mouse models, inducible pluripotent stem cells containing TDP-43 mutations and postmortem CNS brain and spinal cord tissue from ALS and FTLD patients with TDP-43 proteinopathy.The objectives of the project are following:
– Discovery of RBPs that bind to TDP-43 mRNA and GGGGCC repeat RNA.
– Functional characterization and disease relevance of selected RBPs.
– Tool for detection and diagnostics of GGGGCC repeat RNA.

Further information available at:

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