Does stress induced reduction of translational fidelity play a role in ALS/FTLD?

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Recent genetic and pathological discoveries have placed the TAR DNA binding protein 43 (TDP-43) at the center stage in the pathogenesis of amyotrophic lateral sclerosis (ALS). In 95% of the patients with ALS, TDP-43 accumulates in the cytoplasm of motor neurons forming large hallmark aggregates. However, only in a very small percentage of cases is this aggregation caused by TDP-43 mutations. Therefore, one of the main questions in the research field is which disease related changes make ''normal'' TDP-43 aggregate in ALS. *In vitro* and *in vivo* experiments have shown that TDP-43 is prone to aggregation, therefore any changes in transcription, translation, post-transcriptional modification, localisation and/or degradation of TDP-43 that influence the steady-state level of TDP-43 protein at a specific location, may give a pathological outcome. Cellular stress is known to affect any of the above mentioned stages in protein synthesis/degradation, which may have consequences at the level of the organism. For example, oxidative stress in cells, has been associated with ageing and pathogenesis and progression of many neurodegenerative diseases. Recently it has been shown that stress can also lead to a decrease in translational fidelity through incorporation of wrongly-coded amino acids into the protein sequence. Cellular stress can lead to a hundred fold increase in misacylation of tRNAs (i.e. tRNAs bind to wrong amino acids) resulting in changes in protein sequence, which may have an effect on the function and stability of the protein. In a preliminary study we have shown that under conditions of oxidative stress TDP-43 undergoes changes in its isoelectric point, which cannot be explained by phosphorylation suggesting changes in amino acid sequence as one of the possible causes.

In this one year pilot project we will explore, using cellular models of oxidative stress and mass spectrometry, if these stress-related sequence changes occur in TDP-43 protein and to what extent can they be detected in post-mortem spinal cord tissue from ALS patients. Confirmation of this amino acid 'misincorporation' phenomenon will have important implications in understanding the pathogenesis of ALS.

The research will be done at the Jozef Stefan Institute in Ljubljana, Slovenia. Within the institute there is a Centre of Excellence for Integrated Approaches in Chemistry and Biology of Proteins, which includes a state of the art proteomics facility that would be used in this project.

Boris Rogelj is senior research associate at Jozef Stefan Institute since 2012. He previously worked at King's College London in the group of Prof. Christopher E. Shaw. His major scientific achievements come from functional characterisation of TDP-43 and FUS proteins in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD): "*We identified neighbouring mutations in a highly conserved region of TDP-43 (Sreedharan J, Science 2008) and FUS (Vance CA, Science 2009) in sporadic and familial ALS cases. They are both predominantly nuclear proteins that are implicated in processing and transport of RNA. The two publications in Science are among the top 1% of most cited publications in neuroscience in the last two or three years respectively (source WoS).*

We have also characterised the nuclear transport (Nishimura A, Brain 2010) of TDP-43 and RNA binding properties of TDP-43 (Tollervey JR, Nat Neurosci 2011) and FUS (Rogelj B, Scientific Reports in press). In addition, we have neuropathologically characterised optineurin in the context of ALS and FTLD (Hortobagyi T, Acta Neuropath 2011) and discovered that specific TDP-43-negative and abundant p62-positive staining of hippocampal and cerebellar neurons is a major neuropathological feature for ALS/FTLD associated with newly discovered disease-associated hexanucleotide repeat in C9orf72 gene (Al-Sarraj S, Acta Neuropath 2011; Troakes C, Neuropathology in press). In a global analysis of alternative splicing changes in aging and neurodegeneration we discovered some correlations between the two processes (Tollervey JR, Genome Res 2011)."