RNA decay in amyotrophic lateral sclerosis and frontotemporal lobar degeneration

https://neurodegenerationresearch.eu/survey/rna-decay-in-amyotrophic-lateral-sclerosis-and-frontotemporal-lobar-degeneration-2/

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Country

USA

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RNA decay in amyotrophic lateral sclerosis and frontotemporal lobar degeneration

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01/08/2016

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5

The project/programme is most relevant to:

Motor neurone diseases|Alzheimer's disease & other dementias

Keywords

RNA Decay, Frontotemporal Lobar Degenerations, Amyotrophic Lateral Sclerosis, neuronal survival, induced pluripotent stem cell

Research Abstract

Abstract Maintenance of RNA homeostasis involves a dynamic balance between RNA synthesis

and turnover. This balance is critical for transcriptionally active cells such as neurons, as disruptions to any individual component can lead to RNA misprocessing and cell death. Our preliminary evidence indicates that deficiencies in RNA decay represent a fundamental and heretofore unrecognized mechanism driving neuronal dysfunction and death in the neurodegenerative diseases amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Our goals with this proposal are to elucidate the role of RNA decay in the pathogenesis of ALS and FTLD, and investigate a unique and promising therapeutic strategy affecting RNA decay. Based upon the results of initial studies, we propose that in ALS and the most common subtype of FTLD, characterized by neuronal deposits of the RNA binding protein TDP43, RNA homeostasis is disrupted by an inappropriate interaction between TDP43 and the RNA helicase UPF1, ultimately resulting in neurodegeneration. We will test this model by i) determining the impact of the TDP43-UPF1 interaction on neuronal survival and RNA decay, ii) evaluating if deficient RNA decay is sufficient and/or necessary for pathologic TDP43 deposition in neurons, and iii) assessing whether UPF1 expression improves neuronal survival by restoring TDP43 and RNA homeostasis. We will pursue these aims using a combination of longitudinal single-cell microscopy of human neurons derived from ALS and FTLD patients, CRISPR/Cas9 genome editing and high-throughput sequencing of pulse-labeled RNA. The multifaceted approach proposed here promises to uncover key pathways controlling neuronal survival in healthy cells and in those affected by ALS and FTLD, and will bring us one step closer to achieving our long-term goal of developing an effective treatment for these and other relentlessly progressive neurodegenerative disorders.

Lay Summary
Project Narrative This proposal focuses on the contribution of RNA decay to neuronal dysfunction and death in the neurodegenerative diseases amyotrophic lateral sclerosis and frontotemporal lobar degeneration. The investigations described here will uncover essential connections between the RNA binding protein TDP43, RNA decay and neurodegeneration that can be leveraged into novel therapeutic strategies. We will also elucidate the mechanism of action of UPF1, a potent neuroprotective agent that has shown promise in disease models.

Further information available at:

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Investments > €500k

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