Deciphering the mechanisms of TDP-43 and FUS/TLS mediated neurotoxicity

https://neurodegenerationresearch.eu/survey/deciphering-the-mechanisms-of-tdp-43-and-fustls-mediated-neurotoxicity/

Name of Fellow

Polymenidou Magdalini

Institution
Funder

SNSF

Contact information of fellow
Country

Switzerland

Title of project/programme

Deciphering the mechanisms of TDP-43 and FUS/TLS mediated neurotoxicity

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01/09/13

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4.0

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Protein misfolding | RNA-binding proteins | Amyotrophic lateral sclerosis | Neurodegeneration | Prion-like spreading | Frontotemporal lobar degeneration

Research Abstract

This proposal aims to understand the neurotoxic mechanisms triggered by the aggregation and functional interruption of TDP-43 and FUS/TLS, two RNA/DNA-binding proteins integrally involved in the pathogenesis of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). I plan to use toxic aggregates of TDP-43 and FUS/TLS, either derived from postmortem patient material, or reconstituted in vitro using purified components, to establish a novel ex vivo model for TDP-43- and FUS/TLS-mediated neurodegeneration in mouse organotypic brain and spinal cord slice cultures. With this system, I will determine the neurotoxic pathways triggered by the induced aggregation of TDP-43 and FUS/TLS, using both unbiased high-throughput sequencing transcriptomic analysis and candidate approaches, and will investigate the role of glial cells in the cell-to-cell spreading of aggregation and toxicity. Lastly, I will establish the relevance of the uncovered mechanisms for human disease by testing them in iPS cell-derived human neurons from ALS patients and healthy controls.

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Fellowships

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