Investigating a neuronal subcellular transcriptome by the novel technique of RNA TU-tagging, in a normal and ALS-related mouse model.

https://www.neurodegenerationresearch.eu/survey/investigating-a-neuronal-subcellular-transcriptome-by-the-novel-technique-of-rna-tu-tagging-in-a-normal-and-als-related-mouse-model/

Principal Investigators

Professor E Fisher

Institution

University College London

Contact information of lead PI
Country

United Kingdom

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Investigating a neuronal subcellular transcriptome by the novel technique of RNA TU-tagging, in a normal and ALS-related mouse model.

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Motor neurone diseases

Keywords
Research Abstract

Coding and non-coding RNAs are transported to different subcellular localisations for local translation and regulation. Localised ‘RNA metabolism’ is important in polarised cells such as neurons, but techniques to study RNA localisation are not able to isolate subcellular transcriptomes in vivo. Motor neurons (MNs) have cell bodies in the spinal cord, numerous arborizing dendrites and they connect to muscle fibres at the neuromuscular junction (NMJ) through an axon that can exceed 1 meter in length. We are interested in MNs because of our research into Amyotrophic Lateral Sclerosis (ALS), a fatal neurodegenerative disorder that is characterized by the progressive loss of motor neurons that ‘die back’ from NMJs. ALS-causative mutations in RNA-binding and -transport genes (TARDBP ‘TDP-43’, FUS), and in C9ORF72 that induce RNA foci – have highlighted aberrant subcellular RNA metabolism in ALS pathogenesis. Thus there is a clear need to identify the neuronal subcellular transcriptome in vivo to understand normal function, and dysfunction in our paradigm disease, ALS. We will use a new technique, ‘TU-tagging’ (already successful in mouse) to identify the subcellular transcriptome of three compartments of adult motor neurons in normal mouse and in a mouse with a mutation in Tdp-43. Our preliminary data from a Tdp-43 mutant we are characterising shows disruption of many downstream genes including b-synuclein and tau. TU-tagging works through the cell-specific expression of an enzyme (UPRT) and treatment with a drug (4TU), allowing incorporation of thio-uridine into RNA in specific cell types. Thio-uridine RNA is biotinylated and then pulled-down. We will use TU-tagging to identify RNA from (1) MN cell bodies and dendrites, (2) MN axons, (3) NMJs. This will allow us insight in the biology of MNs, axons and NMJs and their susceptibility in disease. TU-tagging is applicable to all models of normal function and disease, and of neuronal injury.

Lay Summary
Further information available at:

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