Investigating deficits of axonal RNA metabolism and axonal signalling in amyotrophic lateral sclerosis

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Name of Fellow

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Institution
Funder

MRC

Contact information of fellow
Country

United Kingdom

Title of project/programme

Investigating deficits of axonal RNA metabolism and axonal signalling in amyotrophic lateral sclerosis

Source of funding information

MRC

Total sum awarded (Euro)

€ 1,567,535

Start date of award

01/04/15

Total duration of award in years

4.0

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Amyotrophic lateral sclerosis | axon | Fused in sarcoma | Motor neuron disease | RNA

Research Abstract
Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a relentlessly progressive neurodegenerative disorder, which causes loss of motor neurons (MN) leading to paralysis and ultimately death. It is currently untreatable, hence there is a desperate need for understanding its underlying mechanisms to develop novel and effective therapeutic strategies. Published research and preliminary data show that: 1) RNA metabolism alterations play a role in ALS; 2) MN axons are affected in the early stages of disease; 3) axonal RNA transport is altered in ALS and deficits in axonal RNA localisation make axons more susceptible to noxious stimuli; 4) key ALS proteins associate with signalling endosomes (SEs), endosomal organelles which are responsible for axonal signalling and transport of survival messages. These observations converge to define my research questions. I will investigate: a) the axonal RNA changes occurring in ALS; b) the mechanisms contributing to these changes, with a focus on RNA stress granules (cytoplasmic bodies, altered in ALS, where RNAs are protected during cell stress); c) the novel link between key ALS proteins and axonal signalling. In order to do so, I will combine the cutting edge tools and unique resources available in my Sponsor’s laboratory and through collaborators. I will isolate MNs from a unique novel ALS mouse model which expresses an aggressive ALS-causative FUS mutation at physiological levels. I will then use microfluidic chambers and the UPRT RNA tagging technology in order to specifically isolate axonal RNA from MNs; I will then analyse SEs using magnetic isolation techniques and quantitative proteomics. Finally I will be able to validate my results using differentiated MNs derived from human iPSC isolated from ALS patients. These findings will be further tested in patient tissue and will be paramount for the identification of novel pathways and potential therapeutic targets in ALS.

Types:
Fellowships

Member States:
United Kingdom

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A