Investigating a Toxic Gain-of-Interaction Between FUS/TLS & Stress Granules

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USA

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Investigating a Toxic Gain-of-Interaction Between FUS/TLS & Stress Granules

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NIH (NINDS)

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01/04/2012

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1

The project/programme is most relevant to:

Motor neurone diseases

Keywords

liposarcoma, sarcoma, Cytoplasmic Granules, Amyotrophic Lateral Sclerosis, RNA-Binding Protein FUS

Research Abstract
DESCRIPTION (provided by applicant): Mutations in the gene encoding Fused in

Sarcoma/Translocated in Liposarcoma (FUS/TLS or FUS) were recently linked to amyotrophic lateral sclerosis (ALS). ALS is the most common motor neuron disorder. The mean age of onset is 55 yrs, and patients generally survive for only 3-5 yrs after diagnosis. Currently there is no cure for ALS. A majority of ALS-linked mutations in FUS/TLS cause this predominately nuclear protein to accumulate within the cytoplasm. To date, it is not clear whether this mislocalization plays a role in ALS pathogenesis, either by inducing a loss of nuclear function and/or by introducing a gain of toxic function within the cytoplasm. Several groups have demonstrated that ALS-linked mutant FUS proteins incorporate into cytoplasmic stress granules in response to applied stress. Conversely, the wild-type FUS protein remains nuclear and largely excluded from stress granules. Stress granules are stalled translational complexes that function to restore cellular homeostasis after a stress-induced event; stress granules are a normal and necessary response to stress. Our hypothesis is that the association of ALS-linked mutant FUS with stress granules represents a toxic gain-of-interaction that impairs the function of these granules, thus compromising both cellular stress response and homeostasis in ALS. The aims of this proposal will determine if the association of mutant-FUS with stress granules alters their functional properties (e.g., rate at which these stress granules assemble and disassemble in response to induced stress) using microscopic methods. Quantitative proteomics will be used to examine whether mutant- FUS alters cellular stress response (i.e., the protein translation profile in the cell during applied stress and stress withdrawal). The mechanism of mutant-FUS incorporation into stress granules will be investigated, since it will be important to understand this process fo future therapeutic purposes. Motor neurons derived from ALS patient induced pluripotent stem (iPS) cells and ALS-transgenic mice will be employed to investigate the effects of mutant-FUS associated stress granules on cellular homeostasis. Importantly, these aforementioned studies will allow us to address whether mutant-FUS incorporation into stress granules is in fact toxic and thus potentially causative for disease. The link between FUS, stress granules and ALS pathogenesis will be further investigated by probing for elevated stress granule markers within human patient samples. These studies have the potential to reveal stress granules as biomarkers of ALS.

Lay Summary

Mutations in a protein called FUS/TLS cause ALS or Lou Gehrig’s disease, a devastating motor neuron disease for which there is no cure. There is evidence that mutated FUS/TLS has an adverse affect on cellular stress response, which can potentially lead to cell death. This proposal will investigate whether FUS impairs stress response.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Motor neurone diseases

Years:
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