Investigating the response of FUS/TLS to excitotoxic insult

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Amyotrophic Lateral Sclerosis, excitotoxicity, RNA-Binding Protein FUS, Glutamates, liposarcoma

Research Abstract

? DESCRIPTION (provided by applicant): Fused in Sarcoma/Translocated in Liposarcoma (FUS/TLS or FUS) is a multifunctional, RNA/DNA-binding protein that is pathologically associated with amyotrophic lateral sclerosis (ALS). The role of FUS in this disorder has not been elucidated, although evidence exists to support both a loss of normal FUS function and gain of toxic function mechanisms. We have identified a novel, normal response of FUS to

excitotoxic levels of glutamate in primary neurons. Our preliminary data demonstrates that endogenous FUS translocates from the nucleus to the cytoplasm in response to sublethal but excitotoxic levels of glutamate. Glutamate excitotoxicity is strongly implicated in ALS, and therefore we believe these finding are relevant to disease pathogenesis. We posit that FUS plays a normal and protective role in response to excitotoxicity, which is a form of cellular stres. Our hypothesis is that FUS functions in the context of protein translation in response to excitotoxic stress. This response may be impaired by ALS-causing mutations, thereby exacerbating the severity of excitotoxicity in FUS-mediated ALS. Moreover, chronic excitotoxicity may contribute to the accumulation and subsequent aggregation of the FUS protein in diseased neurons. The Aims of this proposal will investigate the response of FUS to excitotoxic levels of glutamate in neurons and determine if ALS-linked mutations alter this response.

Further information available at:

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