How Light-Controlled FUS Aggregation Can Help Model ALS/FTD

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Abstract:

The formation of toxic protein deposits in neuronal and glial cells is a hallmark of many neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). FUS is one of the causative genes for familial ALS, and most ALS-linked mutations disrupt its nuclear localization signal, leading to cytoplasmic accumulation and the formation of inclusions. FUS inclusions are also detected in patients with the related neurodegenerative disorder FTD. However, unlike in ALS, FUS inclusions in FTD occur without any known mutation in the FUS gene.

FUS is an RNA-binding protein essential for transcription, splicing, and DNA repair, and naturally undergoes phase separation through its disordered N-terminal domain (IDR). However, the mechanisms by which physiological FUS assemblies transition into pathological aggregates remain poorly understood, in part because many cellular and animal models fail to recapitulate FUS aggregation.

To address this limitation, we developed an optogenetic system that enables spatial and temporal control of FUS aggregation using the light-responsive Cry2olig domain from Arabidopsis thaliana. We generated light-inducible constructs for wild-type FUS, the ALS-linked P525L mutant, and the isolated FUS IDR. After validation in HeLa cells, we established stably expressing SH-SY5Y cell lines to provide a reproducible model for inducing and studying FUS aggregation under controllable conditions. This optogenetic platform offers a versatile tool to investigate the dynamics and determinants of FUS aggregation in ALS/FTD-related contexts.