| | |
|---|---|
| First Author: Joseph-Patrick Clarke (Postdoctoral) | Poster Session: pm |
| Presenting Author: Joseph-Patrick Clarke (Postdoctoral) | Location: 1 |
| Mentor/Lab: Christopher Donnelly | Category: Neurology & Neurodegenerative Diseases |
| Department: Neurobiology | |

Title: Inducing Stress Granule Formation Using Optogenetics

Summary: The goal of this work is to generate light-induced SGs to study the role of these membraneless organelles in ALS/FTD. Our work is the first to report the formation of functional membraneless organelles using light and demonstrates spatial and temporal control in their formation in the absence of cytotoxic cell stress. Employing this method allows us to broaden our understanding of the pathobiology underlying ALS and FTD and their neuropathologies.

Abstract: Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) are progressive fatal neurological diseases caused by the loss of upper and lower motor neurons or cortical neurons respectively. The majority of diagnosed ALS and FTD patients are classified as having a sporadic phenotype with the remaining considered familial based on patient history. A molecular similarity between both neurological diseases is the observed cytoplasmic aggregation of the RNA-binding proteins TDP-43 and FUS in post-mortem tissue samples. Current hypotheses suggest that impaired homeostasis of cell stress activated cytoplasmic granules called stress granules (SGs) may serve as sites of TDP-43 and/or FUS aggregation in disease and thus may promote disease progression. SGs form under periods of cell stress and function to prevent global protein synthesis to promote the upregulation of stress response genes until the stress is removed. Elucidating such an effect however has been problematic using current methods to form stress granules since prolonged treatment with extracellular stress is cytotoxic thus preventing the study of prolonged or repetitive stress granule formation on in the induction of ALS/FTD neuropathology. To overcome this we developed a novel method employing light-induced protein clustering to seed the core protein components. The goal of this work is to generate light-induced SGs to study the role of these membraneless organelles in the absence of toxic extracellular stressors. Employing this method we are able to broaden our understanding of the pathobiology underlying ALS and FTD and their neuropathologies. Our results demonstrate that the light induced SGs co-localize with endogenous stress granule components including G3BP1 Ataxin-2 PABPC1 TIAR and eIF3H. Additionally the light-induced SGs sequester mRNAs and translation factors to inhibit global protein synthesis similar to endogenous SGs. Light-induced SGs can be controlled to induce prolonged or repetitive SG formation and light-induced SGs sequester with the ALS/FTD proteins TDP-43 and FUS. This body of work allows us to form functional SGs with great spatial and temporal control and in the absence of cytotoxic cell stress. This is the first report of the formation of functional membraneless organelles using light. We are currently using this tool to elucidate the role of SGs in TDP-43 and FUS aggregation and in ALS/FTD pathobiology.