Inhibition Of Stress Granule Formation Through Manipulation Of UBAP2L

Published date: June 23, 2018

Technology description

Researchers from UC San Diego have developed a method to reduce stress granules (SG) and related protein aggregation by lowering expression levels or simply deleting a small portion of UBAP2L. UCSD bioengineers were able to deplete UBAP2L by small interfering RNA (siRNA) in HeLa cells and almost completely abolish NaAsO2-induced SG formation, establishing UBAP2L as an essential regulator of SG assembly.

Stress granule (SG) formation has been suggested as a two-step process, with initial formation of a dense stable SG ‘‘core’’ followed by accumulation of proteins containing intrinsically disordered regions (IDRs) and low-complexity domains (LCDs) into a peripheral ‘‘shell’’ through a process involving liquid-liquid phase separation (LLPS). Recently, SGs have been associated with human neurodegenerative disorders characterized by the presence of toxic insoluble protein aggregates. This link is most compelling in the case of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), where numerous disease-causing mutations are purported to interfere with LLPS-dependent growth and dynamics of SGs.

Advantages

This is an improvement over similar attempts to reduce SG formation because previous approaches employed proteins with known disease-association and critical functions in neuronal cells. UBAP2L may be less functionally critical, as suggested by minimal effects on cell viability upon UBAP2L knockout. A second significant improvement over previous approaches is the technology’s ability to affect SG levels through targeted deletions within UBAP2L, thus not requiring a loss of function of the entire protein.

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