Exploring the toxicity of aggregates associated with protein-misfolding diseases

https://www.neurodegenerationresearch.eu/survey/exploring-the-toxicity-of-aggregates-associated-with-protein-misfolding-diseases/

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Country

USA

Title of project or programme

Exploring the toxicity of aggregates associated with protein-misfolding diseases

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NIH (NINDS)

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€ 1,370,123.85

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01/08/1997

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3

The project/programme is most relevant to:

Motor neurone diseases|Huntington's disease

Keywords

protein TDP-43, protein misfolding, Toxic effect, Yeasts, Prions

Research Abstract

? DESCRIPTION (provided by applicant): Many neurodegenerative conditions including Alzheimer’s, Parkinson’s, prion and Huntington’s diseases are associated with specific protein

aggregates that form as a result of protein misfolding. To prevent or treat these conditions we must understand what causes the proteins to aggregate, and how this is associated with pathology. These questions will be addressed using yeast, neuroblastoma cells and primary cortical neurons expressing FUS and TDP-43 as cellular models of Amyotrophic lateral sclerosis and Fronto-temporal dementia. The conservation in cells from yeast to human neurons of cellular pathways such as protein refolding, the ubiquitin proteasome system, secretion, vesicular trafficking, and autophagy, has allowed yeast with its powerful experimental toolbox, short generation time, and well-characterized genome, to address aspects of neurodegenerative disease that involve these fundamental systems. This has provided new insight into protein misfolding neurodegenerative disease. Many human proteins that aggregate and are associated with neurodegenerative disease, also aggregate and are toxic when expressed in yeast. Modifiers of this toxicity identified by genetic screens in yeast have been shown, remarkably, to be new or previously known human disease risk factors. In aim I, newly designed high-throughput screens in yeast will identify novel genetic modifiers that enhance or suppress toxicity of TDP-43 or FUS. Homologs of these modifiers will then be tested for similar effects in neuroblastoma cells and primary neurons and screened for mutations in patients. Aim I also explores the mechanisms of action of known modifiers by: determining which domains of the Hsp40 chaperone Sis1 are required in order for Sis1 overexpression to rescue cells from FUS or TDP-43 toxicity; testing the hypothesis that over- expression of ATXN2, a stress granule polyQ expansion protein, enhances TDP-43 toxicity by increasing TDP- 43's titration of Sis1, thereby reducing Sis1 mediated delivery of ubiquitinated proteins to the proteasome; testing if overexpression of the Hsp104 chaperone, reduces toxicity by trimming aggregates from their ends via chaperone imbalance; determining if TDP-43 or FUS aggregates are toxic because they co-aggregate with essential proteins thereby inactivating them. This aim has the potential to identify new human disease susceptibility genes and therapeutic targets. The goal of aim II is to establish and characterize different heritable TDP-43 con- formational variants in yeast and neuroblastoma cells and to test their pathogenic effects on primary cortical neurons. This aim builds on our new discovery that TDP-43 can propagate as a prion in yeast. Identifying con-formational variants of TDP-43 is important because different variants are likely to affect disease progression and symptoms differently. As cross-talk between heterologous proteins can enhance de novo aggregation, aim III uses a candidate and screen approach to find mammalian proteins with the ability to enhance de novo aggregation of TDP-43 and FUS. Also aim III examines the effects of stress on de novo aggregation of TDP-43 and FUS. Under- standing how cross-talk and stress influence TDP-43 and FUS aggregation may lead to therapies that inhibit aggregation.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis and Frontotemporal dementia are associated with the formation specific protein aggregates that form as a result of protein misfolding. We study factors that influence the toxicity of these aggregates using yeast, mammalian neuroblastoma cell, and primary cortical neuron models. As such model systems have successfully identified human misfolding disease risk factors, it is likely that insights gaind here about aggregate genesis and causes of toxicity will be applicable to human disease.

Further information available at:

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Investments > €500k

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United States of America

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Huntington's disease, Motor neurone diseases

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