Protein Aggregation and Inclusion Body Formation

https://neurodegenerationresearch.eu/survey/protein-aggregation-and-inclusion-body-formation/

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Country

USA

Title of project or programme

Protein Aggregation and Inclusion Body Formation

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,734,847.71

Start date of award

01/07/2012

Total duration of award in years

1

The project/programme is most relevant to:

Huntington's disease

Keywords

Inclusion Bodies, protein aggregation, Huntington gene, Ubiquitin, protein aggregate

Research Abstract
DESCRIPTION (provided by applicant): Accumulation of protein aggregates and ubiquitin (Ub) into cytoplasmic inclusion bodies (IB) is the single most definitive diagnostic neuropathological marker of neurodegenerative disease. Despite this universal diagnostic significance, the cell

biological mechanisms underlying IB formation and, indeed, whether formation of these structures reflects a pathogenic or protective process, remains an unresolved mystery. The long-term objective of this research project is to elucidate the molecular mechanisms that underlie IB formation and Ub deposition and to develop an integrated understanding of how mammalian cells respond to the chronic expression of pathogenic, aggregation-prone proteins. The research supported by this project during the previous funding period exploited single-cell analysis of a cellular model of Huntington’s disease (HD) to show that, although mature IB contain both aggregated huntingtin (htt) and Ub, the two proteins are recruited to IB with vastly different kinetics. These observations, together with emerging data from genetic models of neurodegenerative disease, suggest a model in which chronic expression of a folding-defective aggregation-prone protein like htt, burdens the cell’s proteostasis capacity (ie, the cell’s ability to maintain the correct dynamic equilibrium between protein folding and degradation) leading to a progressive diversion of normal proteins from productive folding to the ubiquitin proteasome system, ultimately overwhelming the cell’s capacity to degrade proteins. The research in this proposal aims to rigorously testand refine this emerging model using state-of-the-art proteomic and bioimaging technologies. These studies will provide a comprehensive understanding of the dynamic interaction between protein aggregation and proteostasis and will illuminate one of the longest-standing controversies in neurodegenerative disease biology.

Lay Summary

The aging of the US population portends an epidemic of neurodegenerative disorders. Emerging research suggests that these diseases are closely associated with the capacity of brain cells to resist the stress of protein synthesis, folding and degradation. The proposed research will exploit state-of-the-art methodology to understand how cells deal with these stressors using a powerful genetic model of neurodegeneration, and will provide important insights into the development of new therapeutic targets and biomarkers.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

Database Tags:
N/A