Toxic protein aggregation in neurodegeneration

https://neurodegenerationresearch.eu/survey/toxic-protein-aggregation-in-neurodegeneration/

Principal Investigators
Institution
Contact information of lead PI
Country

European Commission

Title of project or programme

Toxic protein aggregation in neurodegeneration

Source of funding information

European Commission FP7-Seventh Framework Programme

Total sum awarded (Euro)

€ 13,927,098

Start date of award

01/06/2013

Total duration of award in years

6.0

The project/programme is most relevant to:

Neurodegenerative disease in general

Keywords
Research Abstract

Formation of amyloid-like protein aggregates is the hallmark of a number of neurodegenerative diseases, but how the aggregation process is linked with cytotoxicity and cell death remains unclear. The goal of this pro¬ject is to elucidate the basic mechanisms of aggregate toxicity and how it affects the biological system in its entirety. We will analyse cell culture and mouse models of Huntington's disease, amyotrophic lateral sclero¬sis and Alzheimer's disease using a trans-disciplinary approach combining cellular biochemistry, quantita¬tive proteomics and 3D cryo-electron tomography. The effects of aggregating protein species (APS) formed by designer proteins and authentic disease proteins will be compared to define general and disease-specific toxicity mechanisms. The main aims of this project are:
1. To determine the sequence of cellular events occurring during toxic protein aggregation. Live cell imaging and single molecule fluorescence fluctuation measurements will be employed to

monitor how APS evolve from diffusible oligomers to large inclusions and quantitative proteomics will define signatures for cells with different forms of aggregates.
2. To identify the mechanisms of aggregation toxicity through a systematic interactome analysis of APS in cell culture and mouse brain. The cellular localization of APS and their potential association with membrane structures and cellular machinery will be determined by cryo-ET.
3. To elucidate why cellular protein quality control fails in neurodegenerative disease. Specially designed proteostasis sensors will be used to monitor the status of the protein folding machinery as aggregate pathol¬ogy develops. The potentially protective pathways of inclusion body formation will be explored using cryo-ET and laser capture dissection coupled with highly sensitive proteomics.
Understanding aggregation toxicity will be invaluable in developing novel therapeutic strategies for some of the most debilitating diseases of our time.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
European Commission

Diseases:
Neurodegenerative disease in general

Years:
2016

Database Categories:
N/A

Database Tags:
N/A