Using naturally-occurring fungal prions as models of neurodegenerative protein misfolding

https://neurodegenerationresearch.eu/survey/using-naturally-occurring-fungal-prions-as-models-of-neurodegenerative-protein-misfolding/

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Country

USA

Title of project or programme

Using naturally-occurring fungal prions as models of neurodegenerative protein misfolding

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

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15/07/2016

Total duration of award in years

5

The project/programme is most relevant to:

Prion disease|Neurodegenerative disease in general

Keywords

yeast prion, Prions, protein misfolding, protein aggregation, Nerve Degeneration

Research Abstract

PROJECT SUMMARY Neurodegenerative disease is a general term to collectively describe the numerous disorders that affect neurons of the brain and spinal cord. These diseases primarily manifest as dementias (mental disorders such as Alzheimer's disease) or ataxias (movement disorders such as amyotrophic lateral sclerosis), and are notorious for their lack of effective treatments. The direct cost to Americans for treating Alzheimer's disease alone is predicted to exceed $1 trillion in the year 2050. This does not include the emotional burden or the unpaid care provided by family members. A common feature of most age-onset neurodegenerative diseases is the accumulation of specific proteins into large aggregates within neuronal cells and tissues. Diseases are frequently characterized by which particular proteins are misfolding and aggregating. In many cases, these proteins form amyloid-like structures, which are highly-ordered filamentous aggregates with increased resistance to quality-control mechanisms. Amyloid structures are particularly threatening because they can self-propagate by recruiting proteins to their filamentous termini, thus they can enable runaway protein aggregation. The naturally-occurring prions (infectious proteins) of the yeast Saccharomyces cerevisiae are prime examples of this type of aggregation. They polymerize into self-propagating amyloid fibers and can spread within yeast populations, thus altering cellular phenotypes epigenetically via protein inactivation. However, unlike mammalian prion proteins that underlie the fatal Transmissible Spongiform Encephalopathies (TSEs), yeast prions are generally tolerated by their hosts, though their precise functions or detriments have been a subject of controversy. We propose using yeast prions as inexpensive and safe models for pathological amyloid formation and propagation. How yeast prion proteins interact with each other and with cellular quality-control machinery will have parallels to pathological aggregation that occurs in neurodegenerative processes. Objectives of our research plan include: 1 – Purify infectious prion amyloid directly from yeast cells and apply biophysical methods to create a structural model of the infectious particles; 2 – Determine how eukaryotic cellular quality-control mechanisms can distinguish and recognize prions and other types of macromolecular protein aggregates for site-specific sequestration; 3 – Determine if naturally-occurring yeast prions have novel functions

Lay Summary
PROJECT NARRATIVE Protein aggregation is common to a broad range of diseases, especially many fatal age-onset neurological disorders. This project uses naturally-occurring prions (infectious proteins) found in the yeast Saccharomyces cerevisiae as models for the protein misfolding and aggregation that are observed in neurodegenerative diseases. The long-term goals of this research are to determine how some proteins pathologically aggregate and elucidate the cellular quality-control mechanisms that protect against protein aggregation.

Further information available at:

Types:
Investments > €500k

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United States of America

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Neurodegenerative disease in general, Prion disease

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