Structural polymorphism in the misfolding and aggregation of expanded polyglutamine proteins

https://neurodegenerationresearch.eu/survey/structural-polymorphism-in-the-misfolding-and-aggregation-of-expanded-polyglutamine-proteins/

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Country

USA

Title of project or programme

Structural polymorphism in the misfolding and aggregation of expanded polyglutamine proteins

Source of funding information

NIH (NINDS)

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€ 1,251,378.90

Start date of award

01/01/2015

Total duration of award in years

4

The project/programme is most relevant to:

Huntington's disease

Keywords

polyglutamine, Genetic Polymorphism, Magic, Huntington gene, Huntington Disease

Research Abstract

DESCRIPTION (provided by applicant): Many devastating neurodegenerative diseases result from protein misfolding that leads to plaques or inclusions containing the misfolded protein. Despite a recognized central role of protein misfolding, we generally lack insight into the causative molecular events, in part due to the complex etiology of diseases like Alzheimer's Disease (AD). Huntington's Disease (HD) and at least eight other neurodegenerative disorders have been traced to a remarkable well-defined mutation occurring across different genes: the expansion of a pre-existing CAG codon repeat. In HD, this leads to expansion of a polyglutamine (polyQ) tract within the huntingtin protein, with expansion beyond a ""threshold"" of ~35 Gln leading to a devastating neurodegenerative disease, with the age of onset dependent on the degree of expansion. HD alone places more than 200,000 Americans at risk of disease, with currently no effective curative or preventative treatments. A dramatic improvement in our knowledge of the misfolding pathway is essential to enable the design of treatments that can ameliorate misfolding, disease onset and toxicity. To address this need, we will deploy state-of-the-art magic-angle-spinning (MAS) NMR spectroscopy. This approach has previously allowed us to characterize various protein aggregates with site-specific and atomic resolution, most recently including an array of polyglutamine-related aggregates. Our past and future success in this endeavor is enabled by an in-depth NMR expertise, exquisite NMR hardware, and highly effective collaborations, which have allowed for key insights into the misfolding process and disease-causing toxicity in HD. Informed by our existing NMR data and mechanistic studies, we hypothesize that there is a critical role for intramolecular collapse into a likely common ß-hairpin conformation. Crucially, this conformational change facilitates self-assembly of the misfolded polyQ into oligomeric and fibrillar aggregates that likely contain a signature structural motif characteristic of the collapsed initial structure. Thus, by studying the misfolded states, we probe the molecular underpinnings of the misfolding by expanded polyglutamine. Using MAS ssNMR we will both characterize and leverage an unusual spectroscopic signature that we hypothesize to reflect a unique internal polymorphism that is characteristic of misfolded polyQ domains. Applying these methods to different disease-related proteins, we test our hypothesis that a common structural mechanism is at work across the polyglutamine disease family. We will examine diseases where previous work suggests qualitative differences in the misfolded structure (and thus misfolding mechanism), and in HD will examine polymorphic aggregates that reportedly have differing toxicities. This work will provide the much needed systematic and detailed characterization of this family of disorders that will not only benefit their treatment, bt will also impact our understanding of structure and toxicity as applied to amyloid-related diseases with more complex etiologies, ranging from AD to various systemic amyloidoses.

Lay Summary

PUBLIC HEALTH RELEVANCE: Several devastating neurodegenerative diseases, including Huntington's Disease, are traced to a seemingly well-defined genetic cause (expansion of a CAG repeat) that leads to misfolding and aggregation of mutant proteins with expanded polyglutamine domains. We propose to use advanced spectroscopic methods to probe this misfolding process and in particular evaluate the conformational variability, or polymorphism, within and among the misfolded states. Such insights are greatly lacking and continue to limit our ability to design effective new treatment strategies across this family of as-yet untreatable disorders that place more than 200,000 Americans at risk of disease.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

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