Protein Self Assembly into Nanoaggregates

https://neurodegenerationresearch.eu/survey/protein-self-assembly-into-nanoaggregates/

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Country

USA

Title of project or programme

Protein Self Assembly into Nanoaggregates

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,412,738.53

Start date of award

01/08/2011

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Nanoarray Analytical Device, self assembly, protein misfolding, Raman Spectrum Analysis, flexibility

Research Abstract

? DESCRIPTION (provided by applicant): Aggregation of amyloid proteins is associated with a wide range of human pathologies termed protein misfolding or deposition neurodegenerative disorders, which include Alzheimer’s, Parkinson’s, and Huntington’s diseases. It has been shown that oligomeric species of amyloid aggregates are neurotoxic. Still, the nature of these

species remains unknown. Despite this importance of oligomeric species with respect to toxicity as well as in normal physiological events, knowledge regarding the molecular mechanisms underlying proteins self-assembly is very limited. The objective of this application is to characterize each oligomer at a level that will allow us to understand the molecular mechanism of the nanoassembly process. However, the fact that oligomers are formed transiently essentially impedes their characterization. To overcome this obstacle, we propose a novel approach in which oligomers of a defined size are assembled on a polymer- based Flexible Nanoarray (FNA), which will enable the use of various methods for their characterization. Based on data obtained during the current funding period, we hypothesize that the self-assembly is driven by increased, size-dependent, intermolecular interaction and stability of the oligomers. To test this hypothesis, we will thoroughly characterize FNA-assembled oligomers by applying a set of single-molecule approaches, combined with detailed computational analyses. Guided by strong preliminary data, we will text our major hypothesis through the following three specific aims: Aim 1) Develop a novel flexible nanoarray approach to measure interactions within oligomers; Aim 2) Directly measure directly the lifetimes of oligomers using a novel, tethered approach; and Aim 3) Demonstrate secondary structural analysis for individual aggregated amyloids using a Tip-Enhanced Raman Spectroscopy (TERS) approach. The rationale for the proposed aims is that understanding fundamental mechanisms of protein misfolding and aggregation has the strong potential to translate into specific approaches to control the aggregation process. These advances are expected to lead to the development of new and innovative preventative strategies and treatments for protein misfolding diseases like Alzheimer’s disease. The application is innovative, because it presents a novel approach to the protein aggregation phenomenon and develops a set of new nanotechnology methods with broad biomedical applications. The proposed research is significant because the findings will lay the foundation for efficient treatments against protein misfolding diseases at the very early stages. Additionally, the availability of oligomers of select sizes assembled as FNAs opens prospects for their use as targets in the development of diagnostic tools such as immunoassays. Moreover, given that oligomers, rather than larger aggregates including fibrils, are considered neurotoxic species, the availability of oligomers with desired sizes will open realistic prospects for the development of efficient immunological preventive, diagnostic, and therapeutic strategies for Alzheimer’s disease, Parkinson’s disease, and other neurodegenerative disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: The work proposed is relevant to public health because unraveling structural and dynamic properties of amyloid oligomers the most neurotoxic species is expected to increase the understanding of molecular mechanisms of Alzheimer’s, Parkinson’s and other protein misfolding diseases. The proposed research will provide knowledge on how pathologies related to protein misfolding develop as well as how to control the aggregation process. Thus, the proposed research is relevant to the part of NIH’s mission that pertains to developing fundamental knowledge that will improve preventive and therapeutic treatments for diseases.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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