Self-association and membrane binding of alpha-synuclein

https://neurodegenerationresearch.eu/survey/self-association-and-membrane-binding-of-alpha-synuclein/

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Country

USA

Title of project or programme

Self-association and membrane binding of alpha-synuclein

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

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Start date of award

01/07/2015

Total duration of award in years

2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract
DESCRIPTION (provided by applicant): Parkinson’s disease is the most common neurodegenerative movement disorder, affecting an estimated 1% of the population aged 65 and older. The protein ?-synuclein is the primary component of Lewy bodies, the neuronal cytoplasmic deposits of aggregated proteins that are the hallmark of Parkinson’s disease. There is compelling evidence that the process of ?-synuclein aggregation is directly related to

Parkinson’s disease pathology. However, the aggregation of ?-synuclein is a complex, heterogeneous process during which multiple oligomeric protein species are populated at various timepoints and persist over a range of timescales, making its complete characterization extremely challenging. Moreover, the relationship between the various molecular species formed in the aggregation process and disease pathology is still an open question, although the direct interaction between oligomeric ?-synuclein and cellular membranes has been implicated. An additional complication comes from two recent publications that provide evidence that the native state of ?- synuclein, long believed to be a disordered monomer, may actually be a partially structured tetramer. Our hypothesis is that both the functional and dysfunctional interactions of AS are modulated by changes in the average conformational or oligomeric ensemble and the dynamic interchange between states within these ensembles. Our research will characterize these ensembles in solution (Aim 1), bound to model membranes (Aim 2), and in living cells (Aim 3), with the goal of determining physical features that are associated with th transition to toxic states. As a consequence of these experiments, we will also determine the relationship between the putative tetramer and monomer forms of AS. To do this, we will use single molecule and time- resolved fluorescence methods. Our experimental approaches have the advantage of allowing for the characterization of ?-synuclein under conditions that favor oligomerization or aggregation without the complication of signal interpretation that accompanies actual self-association of the protein. The results of our investigation will be a comprehensive view of what properties of the solution, membrane, and cellular environment favor self-association of ?-synuclein into toxic structures. Such understanding is critical to the long term goal of our research group to identify potential molecular targets for the development of therapeutics to treat or prevent Parkinson’s disease.

Lay Summary
PUBLIC HEALTH RELEVANCE: There is compelling, although poorly understood, evidence that supports a link between the neuronal protein ?-synuclein and the development of Parkinson’s disease. Here we seek to understand the relationship between the intrinsic dynamics and structures of ?-synuclein in solution and bound to membranes and its propensity to self-associate into toxic structures in disease. This work should provide insight into identifyig relevant targets for the development of therapeutics to treat this debilitating disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

Database Tags:
N/A