Single Molecule Studies of Protein Folding Mechanisms

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Country

USA

Title of project or programme

Single Molecule Studies of Protein Folding Mechanisms

Source of funding information

NIH (NINDS)

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€ 1,516,583.49

Start date of award

01/06/2003

Total duration of award in years

2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

alpha synuclein, protein folding, single molecule, Biophysics, Parkinson Disease

Research Abstract

DESCRIPTION (provided by applicant): The fascinating process by which proteins fold to complex 3-dimensional structures plays critical roles in their myriad functions in cells and organisms, and in misfolding that can lead to disease. Protein misfolding and aggregation

(amyloid formation) are implicated in several diseases such as Parkinson’s and Alzheimer’s diseases, prion diseases, diabetes, and heart disease. Furthermore, recent work supports the intriguing idea that protein amyloids can also have functional roles in biology. Therefore, understanding the mechanisms by which proteins fold is critical to furthering our understanding of basic biology and disease, understanding that could later assist with design of therapeutic strategies in this regard. While much has been learned about protein folding and aggregation, these are extremely complex processes, leaving a host of issues yet to be resolved. One aspect of recent note along these lines is the increasing realization that a spectrum of protein disorder (flexibility) is prevalent in genomes, and that this disorder is often intimately linked to functio and malfunction. For example, monomeric forms of several amyloid-forming proteins have extensive stretches of disordered sequence. Here, we propose to develop and apply novel single-molecule fluorescence methods to take next key steps in furthering our understanding of several of the above aspects. Our work will focus on the Parkinson’s disease-linked protein ?-synuclein, which has multiple putative biological functions. This protein has substantial disorder as a monomer and can fold upon binding to partners, an interesting feature that it shares with many disordered proteins. Although ?-synuclein has been investigated for many years, limited insight has been gained about its complex and dynamic biophysics. By avoiding the averaging inherent in most ensemble experiments, we will probe the complex folding landscape of this system and its natural variants during interactions and aggregation at a resolution not feasible by standard methods. Our innovative work will uniquely combine facets of cutting-edge biophysics, optics, biochemistry, and chemical biology. Overall, the work will result in a new level of understanding of the ?-synuclein system, with implications for better understanding of the biology of neurodegenerative diseases. Furthermore, we will develop and implement combination, state-of-the-art single-molecule tools which will be broadly applicable in studies of a host of other biologically important molecules.

Lay Summary

PUBLIC HEALTH RELEVANCE: We will study the complex biophysics of the Parkinson’s disease-related protein ?-synuclein, including its folding, interaction with partners and aggregation. Insights gained are expected to be valuable for the future design of therapeutic strategies to prevent or reverse such protein misfolding diseases, thus contributing to improving public health. The work will also result in new state-of-the-art tools broadly applicable to a number of biological systems.

Further information available at:

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Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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N/A