Membrane remodeling by alpha-synuclein: implications for function and disease

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Country

USA

Title of project or programme

Membrane remodeling by alpha-synuclein: implications for function and disease

Source of funding information

NIH (NINDS)

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01/09/2015

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

alpha synuclein, Fatty Acids, Membrane, Tube, Micelles

Research Abstract

? DESCRIPTION (provided by applicant): The control of membrane shape and curvature is essential for all cellular membrane remodeling events and aberrations in this poorly understood

process have been linked to a number of diseases. This proposal is based upon the recent discovery that ?-synuclein (?S), a protein involved in the pathogenesis of Parkinson’s disease, can induce membrane curvature and potently remodel cellular membranes into bilayers tubes, micellar tubes and discs. Membrane and fatty acid interaction of ?S is of relevance for the pathological as well as the normal functions of this protein; however the mechanisms by which ?S interacts with membranes and fatty acids in health and by which it can disrupt membrane integrity in disease remain poorly understood. The central goal of this proposal is to arrive at a detailed molecular and structural understanding of how ?S binds to membranes and how this interaction, in turn, affects membrane structure and function in vitro and in vivo. In order to investigate the mechanisms that allow ?S to induce the formation of these remarkably diverse membrane structures, Specific Aim 1 uses a combination of EPR, NMR and cryo-EM based approaches to determine the structures of ?S in complex with membrane tubes and discs. Specific Aim 2 investigates how ?S can interact with mitochondria and liposomes whose lipid compositions mimic those of cellular membranes. These studies will give a first indication of the extent to which ?S can remodel different cellular membranes. This aim will also test whether ?S disease mutants or misfolded, toxic ?S oligomers can compromise membrane integrity by uncontrolled induction of membrane curvature and whether this effect can be further promoted by N-acetylation. Structural changes will be monitored using EM, EPR and NMR while membrane integrity will be assayed using leakages experiments. In Specific Aim 3, we will test the hypothesis that ?S can bind to lipids and fatty acids in similar manners. As part of this aim we will perform structural studies to test whether discs and cylindrical micelles formed with fatty acids have the same structure as those formed with lipids. We will also investigate the mechanism by which free fatty acids can promote the misfolding of ?S. Finally, we will investigate the fatty acid-dependent oligomerization of ?S within cells. These studies will also address the controversy with respect to ?S being a natively unfolded monomer or tetramer in the cell. Collectively, these studies also aim to provide a foundation for understanding ?S’s membrane related roles in normal physiology and Parkinson’s disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: The disruption of a cell’s ability to control the shape, integrity and curvature of its membranes can cause a wide range of diseases. The present proposal seeks to understand how ?-synuclein, a protein that can cause Parkinson’s disease, can normally shape membranes in the cell and how this process can go awry in disease. The results will have implications for our understanding and treatment of Parkinson’s disease and provide new insights into the basic principles that allow proteins to shape membranes.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

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2016

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