Mechanisms of Prion Protein Toxicity

https://www.neurodegenerationresearch.eu/survey/mechanisms-of-prion-protein-toxicity/

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Country

USA

Title of project or programme

Mechanisms of Prion Protein Toxicity

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,940,228.44

Start date of award

01/07/2010

Total duration of award in years

1

The project/programme is most relevant to:

Prion disease

Keywords

PrPSc Proteins, Prions, PrP, Prion Diseases, Toxic effect

Research Abstract

? DESCRIPTION (provided by applicant): Prion diseases are fatal neurodegenerative conditions of humans and animals that have significantly impacted public health and the safety of the food and blood supplies. These disorders are caused by infectious proteins called prions, which propagate themselves by a self-templating mechanism in which PrPSc, the infectious isoform, seeds conformational conversion of PrPC, a normal, neuronal glycoprotein, into additional

molecules of PrPSc. Although this model for prion infectivity is now widely accepted, the cellular and molecular mechanisms by which prions actually cause neurodegeneration remain a mystery. There is a critical need to address this question in order to develop effective treatments for these currently incurable disorders. The long-term goal of this project is to understand how PrPSc, or other misfolded forms of PrP, interact with neurons to impair their structure and function, particularly at the level of the synapse, which is thought to be the initia site of prion-induced pathology. There is now strong evidence that prion toxicity is initiated by binding of PrPSc to PrPC on the neuronal surface as part of the first step in the prion seeding process. However, the subsequent events in the neurotoxic pathway remain unknown. The overall objective of this proposal is therefore to define the mechanisms responsible for PrPSc-triggered, PrPC-mediated neurotoxicity in prion diseases. A major roadblock in addressing this problem has been the lack of an experimentally tractable model system in which prion neurotoxicity can be studied in cell culture. We have now developed such a system, based on the ability of PrPSc-containing samples to cause rapid, PrPC-dependent retraction of dendritic spines on cultured hippocampal neurons. In Aim #1, we will use this system to characterize the key synaptotoxic effects of PrPSc. In Aim #2, we will investigate the roles of PrP-associated ionic currents and PrP-mediated signal transduction pathways in the synaptotoxicity of PrPSc. In Aim #3, we will characterize structural changes in PrPC that may be responsible for PrPC-mediated toxic activities. The proposed studies will provide, for the first time, a detailed pictur, from the level of the synapse to the structure of the PrP molecule, of how prions cause neurodegeneration, a subject that has remained poorly understood because of the lack of suitable cell culture models. This work has wide potential applications in terms of devising therapies for prion diseases, as well as for understanding other neurodegenerative conditions, in particular Alzheimer’s disease, which may share with prion diseases underlying pathogenic mechanisms.

Lay Summary
PUBLIC HEALTH RELEVANCE Prion diseases are fatal neurodegenerative disorders of humans and animals that pose a grave threat to public health, and endanger the safety of the food, blood and organ supplies. This grant application explores the mechanisms by which prions damage nerve cells and their connections. The project sets the stage for development of novel therapeutic approaches based on blocking specific neurotoxic pathways, and it will enhance understanding of other, more common neurodegenerative disorders such as Alzheimer’s disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Prion disease

Years:
2016

Database Categories:
N/A

Database Tags:
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