The prion protein in health and disease (PRIONS)

https://neurodegenerationresearch.eu/survey/the-prion-protein-in-health-and-disease-prions/

Title of project or programme

The prion protein in health and disease (PRIONS)

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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Source of funding information

European Research Council

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2500000

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01-05-2010

Total duration of award in months

60

The project/programme is most relevant to

- Prion disease
- Neurodegenerative disease in general

Keywords

Research abstract in English

Oligomers are toxic in an array of protein misfolding and aggregation (PMA) disorders. However, the chain of events from protein aggregation to dysfunction is poorly understood. Prion diseases are

marked by accumulation of PrPSc, a misfolded variant of wild-type PrPC. PrPC mediates PrPSc neurotoxicity and counteracts toxic PrPC mutants, indicating that a subversion of normal PrPC function may underlie neurodegeneration, and this may not be limited to prion disease. Here, we propose to explore these newly discovered physiological functions of PrPC in three paradigms. We show that PrPC assembles into a multiprotein complex containing a protease; neurotoxic PrPC mutants generate a smaller complex that is uncleaved.

We show that neuronal expression of PrPC is required in trans for long-term myelin maintenance in peripheral nerves. We will therefore investigate the hypothesis that a fragment of PrPC transmits signals crucial for axomyelinic integrity. We show that PrPC physically interacts with both amyloid b and islet amyloid polypeptide and attenuates functional impairment mediated by these peptides. We therefore propose to test whether subversion of normal PrPC function is involved in diverse PMA disorders. We developed an ex vivo model that accurately reproduces major features of prion infections, most notably neurodegeneration. We have identified several unexpected PrPSc-induced cellular stress pathways which may be common to other PMA disorders.

Using this model system, we will clarify the role of PrPC in cell survival pathways and determine the requirement for PrPC in the pathology of other PMA disorders. This proposal capitalizes on provocative recent results and, if successful, will provide valuable insights into PMA toxicity that will go far beyond prion diseases.

Lay Summary