Cellular pathophysiology of prion-mediated neurodegeneration – a model for understanding protein misfolding disorders

https://neurodegenerationresearch.eu/survey/cellular-pathophysiology-of-prion-mediated-neurodegeneration-a-model-for-understanding-protein-misfolding-disorders/

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Title of project or programme

Cellular pathophysiology of prion-mediated neurodegeneration - a model for understanding protein misfolding disorders

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MRC

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€ 665,428

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01/03/2012

Total duration of award in years

4.0

The project/programme is most relevant to:

Prion disease

Keywords
Research Abstract

Prion diseases are fatal neurodegenerative disorders whose pathogenesis is associated with a conformational rearrangement of the normal cellular PrP (PrPC) to abnormal conformers

(PrPSc) which causes neurodegeneration via a poorly defined mechanism. Understanding these mechanisms has key relevance to other neurodegenerative proteinopathies where both prion-like mechanisms and dysfunction of the proteostasis networks have been suggested to be important. My laboratory has demonstrated that dysfunction of the ubiquitin proteasome system (UPS) is an early event in prion disease pathogenesis in vivo, and that beta-sheet rich PrP oligomers potently inhibit proteasome activity in vitro. Work from my last MRC grant yielded a novel cell model where PrP knockdown neuroblastoma cells have been engineered to express an epitope-tagged PrP-chimera (PrP-Ala224MYC). This novel chimera is unique since it supports prion replication, and generates bona fide epitope-tagged PrPSc. We have used this model system to study the earliest events in prion infection. This proposal has five main aims directed at extending the understanding of the cellular pathobiology of prion disease. Our existing PrP-Ala224MYC cell model will be used to map the cellular trafficking pathways of PrPSc with a view to defining how it accesses the cytosol. We will reconstitute neuronal stem cells derived from PrP KO mice with PrP-Ala224MYC, to study prion formation, UPS dysfunction and cytotoxicity in neurons. Detailed biochemical studies will refine our molecular understanding of the inhibitory interaction between misfolded PrP and the UPS. Lentiviral-mediated knockdown of PrP in vivo will determine whether UPS activity can be modulated in neurons as a viable therapeutic target. A proteomic study of the ubiquitinated proteome in prion-diseased brain will identify substrate proteins that accumulate as the disease progresses with the aim of uncovering new pathways that may contribute to cellular toxicity.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Prion disease

Years:
2016

Database Categories:
N/A

Database Tags:
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