Cell Biology: Cellular functions of the prion protein

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Country

United Kingdom

Title of project or programme

Cell Biology: Cellular functions of the prion protein

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MRC

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01/04/2014

Total duration of award in years

5.6

The project/programme is most relevant to:

Prion disease

Keywords
Research Abstract
According to the widely accepted protein-only hypothesis, prions comprise aggregated forms of misfolded host-encoded cellular prion protein (PrPC) generally referred to as PrPSc. PrPC is a glycosyl phosphatidylinositol (GPI)-anchored cell-surface glycoprotein, expressed in most cell types and tissues, but at the highest levels in the CNS and immune system. PrPC is highly conserved in mammals but a precise cellular function remains unclear although multiple

functions have been proposed. However mice, in which the PrP gene has been knocked out, have no overt phenotype and a normal lifespan, but do not propagate prions and are completely resistant to prion disease, indicating that PrPC expression is absolutely required for prion propagation and prion-induced neurotoxicity. Like most GPI-anchored proteins, PrPC is predominantly found at the cell surface in lipid rafts which has led to the suggestion that it may be involved in signal transduction by acting as a cell-surface receptor. Since PrPC lacks a transmembrane domain for transmitting signals from the cell surface to the inside of the cell, much work has been done to identify binding partners that could transmit the signal from the cell surface to the cell interior. A number of putative binding partners have been identified but the biological significance of many of them is unclear since some are only present within the cytoplasm, whereas others are nuclear. Recent evidence has suggested that PrPC acts as a cell surface receptor for A?-oligomers, the molecular species that mediate toxicity in Alzheimer's disease. PrPC is also widely expressed in the immune system where it has been suggested to play a role in homeostasis as well as in the immune synapse and signalling. We have undertaken a reverse genetic approach, utilising alanine mutagenesis, to investigate the regions of PrPC that are required for efficient prion propagation in PK1 cells, a derivative of N2a neuroblastoma cells. This has identified three regions within the unstructured N-terminus as critical for prion propagation: residues 23-25 (KKR, Charge Cluster 1), glutamine 41 and residues 90-111 (Charge Cluster 2). Our aim is now to identify the proteins that interact with these regions. We also aim to develop cells that can efficiently propagate human sCJD and vCJD prions to set up an automated bioassay for human prions that can be used as a therapeutic biomarker. We will also develop a primary neuronal cell assay for prion neurotoxicity that will be applied to isolate and characterise the putative toxic PrP species.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Prion disease

Years:
2016

Database Categories:
N/A

Database Tags:
N/A