Structural studies of prion proteins and their ligand interactions

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Country

United Kingdom

Title of project or programme

Structural studies of prion proteins and their ligand interactions

Source of funding information

MRC

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5.0

The project/programme is most relevant to:

Prion disease

Keywords
Research Abstract
Prion diseases such as variant CJD and BSE involve accumulation of misfolded forms of normally benign host protein (PrPC) in the tissues of the brain. These misfolded, disease-associated forms are known as PrPSc. To understand this switch in structure and to generate material for work on diagnostic and therapeutic aspects of the disease, we have developed recombinant methods for expressing PrP in E. coli. The production of large quantities of protein

have allowed us to make made significant progress in studying the folding and unfolding pathways of human prion protein leading to the identification of several conformational isomers of the protein, in particular ?-PrP, which shares many biophysical characteristics with PrPSc. When ?-PrP is presented as an antigen for the creation of anti-PrP monoclonal antibodies, the resultant antibodies have affinity for native PrPSc. Defining the folding pathway of PrP is crucial to understanding the events leading to the formation of PrPSc. In the case of other amyloidogenic proteins partially structured folding intermediates have been implicated in the destructive aggregation reactions leading to disease. Using NMR techniques to define backbone amide exchange rates we have demonstrated that PrP, unlike other amyloidogenic proteins, does not populate any folding intermediates. This finding portends that native PrPC must unfold before rearrangement to the PrPSc conformation can occur. This finding has been of particular importance in the design of therapeutic strategies for prion disease. Our efforts in screening for potential anti-prion drugs have focused upon the identification of compounds that stabilise PrPC, and hence reduce the pool of unfolded molecules available for conversion to PrPSc.The biological function of PrP remains a subject of much debate; with suggestions that it may play a role in protection from oxidative stress or participate in copper homeostasis. The hypothesis that PrP may be a cupro-protein in vivo has lacked convincing support due to the apparent low affinity with which the protein binds divalent metal ions. Using a combination of fluorescence and NMR techniques we have fully characterized the affinity and location of such sites.||A key objective for the future is to establish a synthetic source of prion infectivity. Although current work indicates that recombinant material may be rendered infectious, the titre appears low suggesting only a minor component is responsible. To mimic the situation in vivo more closely, mature, eukaryotically expressed PrP possessing a GPI anchor and carbohydrate moieties is required. The conversion of this material into a form that possesses high titre prion infectivity would represent the essential model by which the molecular pathogenesis of prion disease could be dissected. The determination of ?-PrP structure is a key element of furthering our understanding of the conformational events that underlie prion diseases. In addition to the solution structure of soluble ?-PrP we wish to map the interaction surfaces that dictate the ordered packing of PrP into fibrillar structures. Structural information on the nature of sub-unit interfaces in fibrillar PrP may assist in the rational design of therapeutics.

Lay Summary
Further information available at:

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Investments > €500k

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United Kingdom

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Prion disease

Years:
2016

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N/A

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