Molecular and phenotypic analysis of human prion strains

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Title of project or programme

Molecular and phenotypic analysis of human prion strains

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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Address of institution of lead PI

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- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

3842950.99

Start date of award

01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Prion disease

Keywords

Research abstract in English

Prion diseases are fatal neurodegenerative disorders that include scrapie in sheep, bovine spongiform encephalopathy (BSE) in cattle, Creutzfeldt-Jakob disease (CJD), Gerstmann-Strdussler-

Scheinker disease (GSS), fatal familial insomnia (FFI), kuru and most recently variant CJD (vCJD) in humans. Their central feature is the conversion of a normal host protein, the cellular prion protein (PrPC), to an abnormal isoform, designated PrPSc. This transition appears to involve only conformational change rather than covalent modification and confers PrPSc with resistance to proteolytic degradation and detergent insolubility. The marked clinical heterogeneity observed in human prion diseases has yet to be explained. However, it has been clear for many years that distinct isolates, or strains, of prions can be propagated in the same host and these are biologically recognised by distinctive clinical and pathological features. It is therefore likely that a proportion of clinicopathological heterogeneity seen human prion diseases relates to the propagation of distinct human prion strains.

Within the framework of the protein-only hypothesis of prion propagation, distinct clinical and neuropathological phenotypes are thought to be determined by the propagation of distinct PrPSc isoforms with divergent physicochemical properties. Understanding how a protein-only infectious agent can encode phenotypic information has been of considerable biological interest. The integrated research projects undertaken here aim to define the molecular basis of prion strain diversity and will provide important structural data for improving the diagnosis of human prion disease, for investigating the epidemiology of human prion disease and for future rational chemo- or immuno-therapeutic approaches to treating human prion disease. The Scrapie Cell Assay enables prion infectivity to be detected and quantified in days rather than much longer time periods required for conventional rodent bioassay and thereby permits the rapid evaluation of purification strategies for rodent prions and investigation of effective strategies for prion decontamination.

Our research activities are encompassed by seven inter-related projects.

1. Purification of denatured mouse RML PrPSc and reconstitution of infectivity studies.

2. Purification of native RML prions and investigation of the structure of the infectious agent.

3. Characterisation of the physicochemical properties of PrPSc associated with distinct human prion strains

4. Analysis of human prion strains in humans and transgenic mice.

5. Investigation of peripheral pathogenesis states in human prion disease

6. Analysis of animal prion strains in wild type and transgenic mice.

7. Mechanistic correlation of PrPSc structure and prion disease phenotype

Lay Summary