Normal cellular function of PrP: study of PrP null mice and conditional gene expression studies

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Title of project or programme

Normal cellular function of PrP: study of PrP null mice and conditional gene expression studies

Principal Investigators of project/programme grant

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Source of funding information

- Medical Research Council

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60

The project/programme is most relevant to

- Prion disease

Keywords

Research abstract in English

There is widespread interest in possible therapies for CJD and related diseases. It has been assumed that PrPSc, the disease associated ‘rogue form’ of one of the body’s normal proteins, prion protein, PrPc is the main neurotoxic molecule in prion disease. However, increasing evidence points to the fact that PrPSc is not directly toxic, but that as yet unidentified transient intermediate forms generated during prion replication and conversion from PrPc to PrPSc are likely to be involved in neuronal dysfunction and death. T this end we targeted the native form of PrP, PrPc in order to remove the precursor for generation of whatever toxic species is killing cells. We first generated transgenic mice in which genetic deletion of endogenous PrPc resulted in animals being able not only to survive long term after prion infection, but they recovered early prion pathology as well as associated learning, behavioural and neurophysiological defects. We have now used a direct therapeutic approach based on our strategy of removing the native PrPc. We have used lentiviral vectors expressing short hairpin RNAs for RNAinterference directed against PrP. We have stereotactically injected these into the hippocampus of prion infected mice and have shown that this approach protects against neuronal loss, and prion replication in the targeted areas, and leads to a highly significant increased survival of 17% in treated animals after even only a single focal injection. We are now optimising the spatial and temporal requirements for PrP knockdown as an effective therapeutic strategy. We are using an empty-lentivirus for mock treatment and also comparing our results to prion infected mice without viral treatment at all.

We are currently evaluating effects of lentiviral treatment on behavioural outcomes including novel object recognition and burrowing behaviours. Early results that RNAi protects against the loss of burrowing behaviour typical of early prion disease.

We are also interested in the mechanisms of neuroprotection resulting from PrP knockout and are looking both at differential gene expression from microarray data and developing an ex-vivo system of organotypic slice culture to allow a systematic functional analysis of the effects of prion infection and PrP knockdown.

Lay Summary

We have established that the normal form of the prion protein is an effective target for treatment in prion diseases using mouse models. We first found that we could cure mice infected with prions by removing the normal form of PrP using a genetically engineered gene switch. We found that the early holes that appear in prion diseased brains disappeared and that the mice survived without symptoms long term. We also found that early memory and motivational problems recovered along with electrical malfunction of the brain. We are using this now to develop a treatment to target PrP as a strategy.

In our group we are using new technologies to deliver this gene treatment to the brain and working to understand the mechanisms underlying the early disease and recovery.