PRP Expression in Schwann Cells is not Required for Transmissible Spongiform Encephalopathy Neuroinvasion

Citation for published version:
Bradford, B, Manson, J, Brophy, P & Tuzi, NL 2007, 'PRP Expression in Schwann Cells is not Required for Transmissible Spongiform Encephalopathy Neuroinvasion' Prion 2007, Edinburgh, United Kingdom, 26/09/07 - 28/09/07.

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Early version, also known as pre-print

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
PrP Expression in Schwann Cells is Not Required for Transmissible Spongiform Encephalopathy Neuroinvasion

Barry Bradford¹, Peter Brophy², Jean Manson¹ and Nadia L. Tuzi³

¹Neuropathogenesis Unit, Roslin Institute, Edinburgh, UK. ²Centre for Neuroscience Research, University of Edinburgh, Edinburgh, UK.

1. Introduction
Transmissible spongiform encephalopathies (TSE) are transmissible neurodegenerative diseases characterised by long incubation periods and characteristic pathology which includes vacuolar spongiform changes, apopotic neuronal loss and astrocytic proliferation in the central nervous system (CNS). A diagnostic feature of these invariably fatal diseases is the presence of a protease resistant isoform (PrPRES) of the host-encoded membrane glycoprotein PrP, of which the protease sensitive isoform (PrPS) is necessary for disease susceptibility. Schwann cells are known to express PrP when associated with co-expressing peripheral nervous system axons and have also been shown to replicate and propagate TSE agent in culture.

2. Objectives
To test the hypothesis that Schwann cells are involved in TSE neuroinvasion, a line of transgenic mice were produced using Cre / LoxP technology in which PrP expression is removed from Schwann cells. We have injected these mice with TSE agents via various routes to determine the difference in incubation period and CNS pathology when compared to wild type mice.

3. Methods
By breeding mice (P2-Cre) expressing Cre under the control of the peripheral myelin Protein Zero (MPZ or P2) promoter (gift from M. Laura Feltri, Milan) and mice possessing LoxP sites flanking the PrP gene (PrPfl/fl), we have generated mice expressing PrP normally, except where P2 is expressed, i.e. myelinating Schwann cells. Mice were challenged with TSE agents 139A and ME7 intracerebrally (i.c.), orally and intraperitoneally (i.p.). Mice were clinically scored for signs of disease and analysed for terminal pathology. Disease incubation period, vacuolation in specific brain areas and presence of Proteinase K resistant PrP were analyzed as indicators of TSE disease.

4. Results

5. Discussion
Characterisation of these mice show that PrP is effectively excised, resulting in a 90 % reduction in PrP expression in axonal lengths of peripheral nerves. This finding is particularly interesting as no differences have been observed in disease susceptibility or ability to traffic the infectious agent to the CNS in these mice. No alteration was seen in either incubation period or end pathology via agents 139A and ME7 after i.c., oral and i.p. challenges. These results suggest that TSE neuroinvasion may occur via peripheral neurons alone with no involvement of peripheral glia despite their contribution to overall PrP expression in peripheral neurons. Also peripheral PrP glycosylation is not required for neuroinvasion and has no impact on strain specific properties such as the final targeting of CNS vacuolation and deposition of PrPSc.

6. Conclusion
Removal of PrP expression in Schwann cells has no effect on TSE neuroinvasion of the two strains studied. We can therefore discount Schwann cells as a viable therapeutic target during the long incubation period between infection and clinical presentation. This study has revealed some very interesting biochemical and cell biological properties of PrP. The results from this study question what role PrP and its glycosylation status may play in disease. These results also offer insights into possible roles for PrP in glial / axonal interaction and cell signalling.

Funding: MRC. e-mail: barry.bradford@bbsrc.ac.uk