compared to WT, may be relevant to its partial resistance to prion disease, however, further analyses are required.

141. Propagation of human sCJD prions in organotypic slice culture

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ABSTRACT

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are neurodegenerative diseases that are invariably fatal. These diseases result from the conversion of the normal prion protein (PrPC) to a misfolded form (PrPSc) that can template itself and spread through the brain, triggering neurodegeneration. TSEs can affect many mammals, including cervids (Chronic Wasting Disease; CWD), sheep (scrapie), cattle (Bovine Spongiform Encephalopathy; BSE), and humans (Creutzfeldt-Jakob Disease; CJD). There are no treatments for any of the prion diseases, despite decades of research. One challenge to finding successful therapies is the fact that PrPSc can exist in a number of different conformations, each of which may have its own biophysical properties and cause distinct neuropathologies, giving rise to unique prion strain phenotypes. Treatments that target only one specific conformational change in may only work for one strain. Ideally, therapy studies for humans should be done with human prion strains. Here we demonstrate the propagation of human prions in prion organotypic slice culture with evidence of associated neuronal loss. Traditionally, prion strains are generated in animals infected with prion disease; however, these are lengthy experiments, often taking several months. By contrast, the prion organotypic slice culture assay (POSCA) can faithfully recapitulate aspects of prion pathology on a shortened timescale of 40–50 days [1,2]. This makes POSCA an ideal method for propagating prion strains. Originally, POSCA was developed to test mouse-adapted scrapie strains in cerebellar slices [2,3]. We have adapted POSCA to sporadic CJD strains from human samples and samples passaged through mice expressing human PrP. We have also adapted the system to whole brain coronal slices. The ability to propagate human prion strains *ex vivo* will allow investigation of human strain-specific properties during pathogenesis as well as development of strain-specific therapeutic interventions. Because POSCA is an open system, it also allows for testing treatments at discrete disease time points without the confounder of blood-brain barrier.

References

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142. Effects of Elk-PrP^{C} expression levels on CWD strain properties

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ABSTRACT

Chronic Wasting Disease (CWD) is a contagious prion disease affecting various species of free-ranging and/or captive cervids on three continents. Species-specific prion protein (PrP^{C}) polymorphisms influence prion conversion into PrP^{CWD}. PrP^{C} amino acid variation can also regulate disease susceptibility to particular prion strains and has been implicated in the diversification of prion strain conformers [1, 2, 3]. Elk and deer PrP^{C} differ at residue E226Q and this amino acid difference has been implicated in the selection of CWD1 and CWD2 prion strains [4]. As PrP^{C} expression has been suggested to affect prion strain evolution [5], we hypothesized that elk PrP^{C} levels affect CWD strain generation. To test this hypothesis, transgenic (tg) FVB mice over-expressing elk PrP^{C} [6] were crossed with *prnp* knock-out FVB mice to generate tg-elk with different PrP^{C} expression levels. Both tg-elk$^{+/+}$ and tg-elk$^{\pm}$ were exposed to white-tailed deer CWD strains (Wisc-1 and H95^{+}) [2, 3]. The H95^{+} strain was a mixture generated on passage of Wisc-1 in deer heterozygous for H95G96 and Q95S96 [2]. Tg-elk$^{+/+}$ mice succumbed to Wisc-1 with a mean incubation period of 116 ± 7 days post infection (dpi) compared to 164 ± 11 dpi for the H95^{+} strain mixture. Consistent with the reduced PrP^{C} expression, the same deer prion strains resulted in longer incubation periods (157 ± 21 dpi and >180 dpi, respectively) when passaged in tg-elk$^{\pm}$ mice. After first passage, transmission of Wisc-1 and H95^{+} in