MECHANISMS OF DEMYELOGINATION IN PRION DISEASE

Joie Lin
Sigurdson Lab
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- progressive, neurodegenerative disorders
- share similarities with age-related neurodegenerative disorders
PRION DISEASE

- neurotoxicity → neuronal death, spongiform encephalopathy
- mechanisms of neurotoxicity still unclear
- protein-only infectious agent, PrP$^\text{Sc}$
- PrP$^\text{C}$ has many functions

![Diagram showing PrP$^\text{C}$ becoming PrP$^\text{Sc}$ and resulting in neuronal death and body dysfunction.](image)
COMMON FEATURES OF PRION DISEASE:

- protein misfolding
- protein aggregates

HUMAN PRION DISEASES
PrP<sup>Sc</sup> plaques

- Sporadic Creutzfeldt-Jakob disease
- Variant Creutzfeldt-Jakob disease
- Gerstmann-Sträussler-Scheinker disease
- Fatal Familial Insomnia

Alzheimer’s disease
Cerebral amyloid angiopathy
Parkinson’s disease
Amyotrophic lateral sclerosis
Huntington’s disease

- Amyloid-β plaques cortex
- Amyloid-β plaques meninges
- α-synuclein substantia nigra
- Ubiquitin inclusions spinal cord
- Poly-Q inclusions striatum
THE ROLE OF PrP\textsuperscript{C} IN PRION DISEASE

N-terminus is linked to toxic signaling

- Δ32-134 mutant → neuronal toxicity
- Antibodies that bind to C-term and prevent N-C interaction in cis → neuronal toxicity

PrP\textsuperscript{C} itself can mediate neurotoxicity, in the absence of PrP\textsuperscript{Sc}

Spontaneous neurodegeneration
G93N-PrP<sup>C</sup> MICE SPONTANEOUSLY DEVELOP NEURODEGENERATIVE DISEASE

G93N-PrP<sup>C</sup> MICE SPONTANEOUSLY DEVELOP NEURODEGENERATIVE DISEASE

There is no PrP<sup>Sc</sup> in the 93N mouse model, but neurotoxicity is still occurring.

PrP<sup>Sc</sup> = infectious agent
IN THE ABSENCE OF PrP$^{Sc}$, HOW DOES PrP$^{C}$ CAUSE NEUROTOXICITY?

PrP$^{Sc}$ = infectious agent
At terminal disease (550 d), 93N brains exhibited decreased (>50%) myelin-associated glycoprotein (MAG) levels.
PrPC AND DEMYELINATION

WHERE IS THE MYELIN LOSS HISTOLOGICALLY?
MYELIN BASIC PROTEIN (MBP) STAINING
PrPC AND DEMYELINATION


Adapted from Mount & Monje. (2017) Neuron

cognitive deficits

In prion disease, oligodendrocytes develop normally and then degenerate due to excitotoxicity.

excitotoxicity = when neurons die from overactivation of glutamate receptors
**AIM 1:** To determine (i) the timing and extent of myelin loss and (ii) the maturity of the oligodendrocyte population in the Prnp$^{93N}$ knock-in mice (homozygous, heterozygous, and WT littermate controls).

**AIM 2:** To compare the PrP interactome in the Prnp$^{93N}$ knock-in mice (homozygous vs. WT littermate controls) and analyze the differences in interacting proteins or pathways involved in myelin homeostasis.
AIM 1 METHODS: DETERMINE THE TIMING AND EXTENT OF MYELIN LOSS AND MATURITY OF THE OLIGODENDROCYTE POPULATION.

Collect brain and spinal cord samples for biochemical and histologic analyses of myelin proteins and oligodendrocyte populations.
AIM 1 METHODS: DETERMINE THE TIMING AND EXTENT OF MYELIN LOSS AND MATURITY OF THE OLIGODENDROCYTE POPULATION.

Characterize and quantify precursor and mature oligodendrocyte populations in the brain.
AIM 2: COMPARE THE PRP INTERACTOME & ANALYZE DIFFERENCES IN INTERACTING PROTEINS/PATHWAYS INVOLVED IN THE CONTROL OF MYELINATION.

WT 93N/93N

- PrP IP: IgG
- PrP IP: IgG

Subtractive proteomics
PrP hits – IgG hits = interacting partner hits

Whole brain lysate
3-4 biological replicates

High-confidence PrP protein-protein interactors
WT or 93N

-log (p-value)

93N / WT ratio (log2)

BRSK1
Vps37c
NMDAR-2B
• excitatory amino acid transporter 2 (EAAT2)
  • sodium-dependent glutamate transporter
  • glutamate = excitatory neurotransmitter

• decreased PrP interactions with EAAT2
  • $\rightarrow$ lack of glutamate reuptake
  • $\rightarrow$ excess glutamate
  • $\rightarrow$ increased excitotoxicity?

EAAT2 TRANSPORTER
DECREASED INTERACTIONS WITH PRP IN THE 93N MOUSE MODEL

NEXT STEPS

• Continue with image analysis (oligodendrocyte markers)
• Investigate EAAT2 levels
  • Plus other glutamate transporters and receptors
SUMMARY

• Prion diseases are progressive, neurodegenerative diseases
• Our mouse model shows that prion neurotoxicity can occur in the absence of prion aggregates
  • Modified PrP$^C$ can be neurotoxic
• In prion disease, we hypothesize that oligodendrocytes (cells responsible for myelinating the CNS) degenerate over time, leading to demyelination
• Christina Sigurdson
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QUESTIONS?
CHRONIC WASTING DISEASE IN CERVIDS
REFERENCES


