Outline

- Properties of TSE and yeast prions
- Structures of TSE and yeast prions
- Properties of chronic wasting disease (CWD)
- Distribution of CWD in North America and the world over time
- CWD and other animals
- CWD and humans
- The future

Prion (Prē̂oon) PrPSc -- Prof. Stanley Prusiner (1982)

- A proteinaceous infectious particle that lacks nucleic acid
- Cause of TSEs: scrapie, CJD, CWD, BSE, etc.
- Requires a normal cellular prion protein (PrPC)
- PrPC and PrPSc are conformers
- PrPC is natively expressed; highly conserved; function?
  - PrPC detergent soluble; monomer; no PK resistance
  - 2’’ structure of PrPC: α-helical, β-sheet, random coil
- PrPSc is a molecular pathogen; no known natural function
  - PrPSc detergent insoluble; multimer; PK resistance
  - 2’’ structure of PrPSc: β-sheet and random coil only
- Variety of alternate isoforms of PrPSc (strains)
- Resistant to conventional forms of inactivation (very stable)

Central Dogma of molecular biology

DNA → RNA → Protein
DNA : Protein 1:1 and onto
DNA carries heritable information in its sequence (covalent)

Revised Central Dogma of molecular biology

RNA → DNA → RNA → Protein
RNA can carry heritable information in its sequence (covalent)
DNA : Protein 1:1 and onto

Prions

DNA → RNA → Protein
Protein carries heritable information in its conformation (β-sheet)
DNA : Protein no longer 1:1 and onto

Transmissible spongiform encephalopathy (TSE)

- Long asymptomatic incubation; short clinical course; death
- Scrapie: sheep and goats endemic to most of the world
- Creutzfeldt-Jakob Disease (CJD): human disease; both heritable and transmissible
- Transmissible mink encephalopathy (TME): 1985 last outbreak; extinct (?)
- Chronic wasting disease (CWD): deer, moose, and elk, endemic to North America and Norway (?)
- Bovine spongiform encephalopathy (BSE): domestic cattle; 0 cases in the UK in 2016; extinct (?)
- “Spontaneous” TSEs found in humans, sheep and bovines

Cartoon of prion replication

Inherited and spontaneous disease

PrPC Replication

"Species" barrier

**Yeast and fungal prions (1994)**

- Non-Mendelian inheritance
- [URE3] from Ure2p, fails to repress transcription
- [PSI+] from Sup35p, fails to terminate translocation
- [PIN+] from Rna1p, primes [PSI+] formation
- [Het-s] from HETs, facilitates heterokaryon incompatibility
- Are biologically functional; most are non-pathogenic
- Not homologous to mammalian PrP^C
- Variants or strains are known

**β-sheet structure (parallel in register)**

Isolated H-bond 4.8 kcal/mol.
In solution H-bond ~ 1.5 kcal/mol.
Covalent C-H bond ~ 100 kcal/mole

**β-helix structure of [Het-s]**

**Cartoon of deer PrPC**

**NMR structure of deer rPrP**

Asparagine linked glycosylation

**PrPC to PrP^C**

PrP^C

PrP^C

“PrP^C”
Threonines in β-helical antifreeze protein

Bioassay of PK sensitive and resistant prions

PrP\textsuperscript{C} polymorphism and classical scrapie

PrP\textsuperscript{C} polymorphisms and atypical scrapie

Proteinase K (PK) cleavage of prions
Properties of chronic wasting disease (CWD)

- Long asymptomatic incubation; short clinical course; death
- Widely distributed throughout the animal’s tissues
- Readily shed in feces, urine and saliva
- Horizontal and environmental transmission
- Remains viable in the environment for at least 2.5 years
- CWD is comprised of a number of prions strains
- 1978 CWD first identified a prion disease
- 1981 first free-ranging elk with CWD
- 1985 first free-ranging mule deer with CWD
- 1990 first free-ranging white-tailed deer with CWD
- 1996 CWD identified in Saskatchewan
- 2000 CWD found in South Korea (Canadian elk)
- 2016 CWD in Norway (Reindeer, Moose, and Red deer)

Examples of CWD in experimentally infected cervids

Photo Credit: Wyoming Game and Fish Department

http://cwd.info.org/photo
Examples of CWD in experimentally infected cervids

Prion distribution in CWD-infected cervids

Prions excreted by CWD-infected cervids

CWD prion propagation

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CWD prion propagation
Worldwide distribution of CWD

Norwegian and Korean CWD are identical to North American CWD

CWD and other relevant animals

- 1st passage of md-CWD transmitted by ic to cattle (38%)
- 1st passage of wt-CWD transmitted by ic to cattle (86%)
- 1st passage of elk-CWD transmitted by ic to cattle (14%)
- Limited amplification in peripheral cattle tissue (0-3%)
- 2nd passage of md-CWD transmitted by ic to cattle (100%)
- CWD-infected pastures do not yield CWD-infected cattle
- Sheep are susceptible to CWD by ic inoculation (25%)
- "Ovinized" mice are susceptible to elk-CWD (ic) (9%)


CWD and humans

- No cases of CJD caused by consuming CWD prions
- “Humanized” mice not infected by ic inoculation of CWD
- Squirrel monkeys infected ic and orally with CWD
- Cynomolgus macaques?

One experiment using US CWD \(\rightarrow\) No (after 10 years)
Oral dosing of 5 brain homogenates over 10-30 days ic using brain homogenate
Another using Canadian CWD \(\rightarrow\) Yes? (in progress)
Oral dosing of muscle tissue over 3 months ic using steel wires


The future of CWD

- Development of area surveillance (aerial surveillance?)
  - CWD incidence increases with age
  - CWD infected does have fewer fawns
- Developing mucosal immunity strategies
  - Prevent shedding?
  - Prevent infection?
- Testing of hunter harvested and farmed animals
  - Simple, fast, sensitive, minimizes human exposure
- Detection in feces
- More research

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