Prions and Prion Disease

Medical Microbiology (BMS 4510)

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Prions

- Causative agents of bovine spongiform encephalopathy ('mad cow disease'), scrapie in Sheep and Kuru (Creutzfeldt-Jakob syndrome) in humans

- Proteinaceous infectious particles (prion)

- Composed of prion protein (PrP^{sc}) and devoid of nucleic acid (particular protein conformation causes disease)
  - Same amino acid sequence but different conformation (alpha helix to beta pleated sheets)

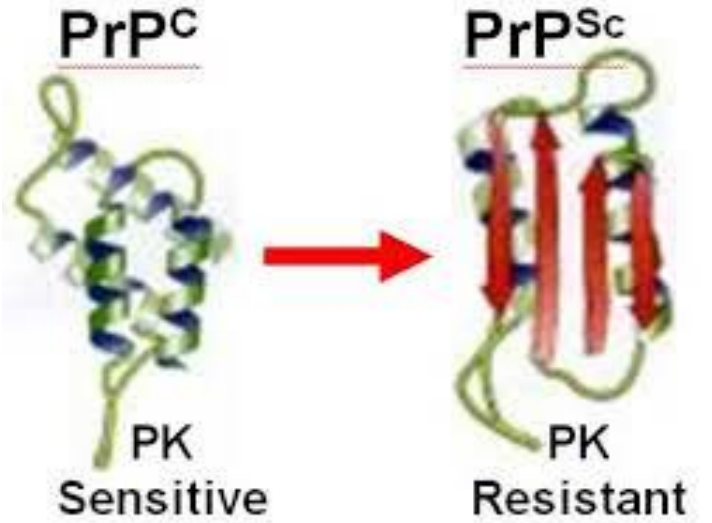
- Highly resistant to physical and chemical agents
- Nonimmunogenic
- Produce slow disease

- **Viroids**
  - Infectious nucleic acids (mostly RNA)
  - Infect plants (no known animal pathogens)

Prions

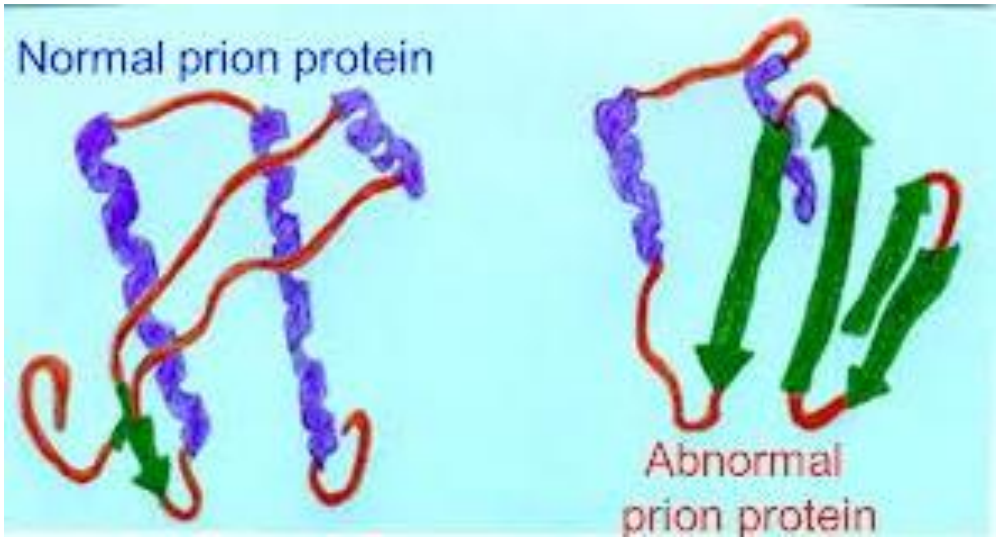
- Prions are oligomers of 33-35kDa proteins (PrP^{sc})
- PrP^{sc} have same amino acid sequence as PrP^{C} found in membranes of neurons but differs in protein conformation.
  - Normal protein has a-helices and scrapie protein has B-pleated sheets
- Spontaneous generation of PrP^{sc} from PrP^{C} occurs by a stochastic event with an incident of 1 per million persons per year.
- PrP^{sc} replicates by forming heterodimers with normal prion proteins, serving as a template for folding of normal prion protein to scrapie conformation.
  - Scrapie protein is highly resistant to proteolysis
  - Reaction proceeds spontaneously and exponentionally (like replication of an infectious agent)
  - Scrapie isoforms accumulate due to resistance to digestion.
- The genes for prion proteins are found in chromosome 20.

PRIONS



A-helical structure

B-pleated structure



Papua New Guinea Highlanders

Subacute spongiform encephalopathies

- Lethal neurodegenerative diseases in human
  - Similar to scapie of sheep and mad cow disease of cows
  - Human diseases: Kuru and Creutzfeldt-Jakob disease

- **Pathology**: basic lesion is a progressive vacuolation in neurons, astrocytes and oligodendrocytes, astroglial hypertrophy and proliferation and spongiform change in grey matter.

- Incubation period of about 3 years
  - Slow disease progression

Kuru

- First described in 1957 in a tribal group of New Guinea Highlands
  - Women and children practiced ritualistic cannibalism of their own deceased relatives
  - Disease declined after custom was stopped but because of the long incubation period, sporadic cases do occur

Creutzfeldt-Jakob disease

- Similar to scrapie of sheep
- Occurs 1 in a million people per year
- Not due to infection; iatogenic transmission
  - Neurosurgery eg cornea or dura matter transplants
- Pathogenesis: Spontaneous generation of PrP^{sc} from PrP^{C}

Papua New Guinea Highlanders