



PRIONS

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Introduction

- Prion are proteinaceous infectious particles, devoid of nucleic acid
- Discovered by Dr. Stanley B. Prusiner
- In 1997, Prusiner was awarded Nobel Prize in Medicine for discovery of infectious proteins (prion) and their mechanism of amplification
- These infectious agents are '**unconventional**' because they are devoid of nucleic acid

Properties of Prions

- Non-immunogenic, evoke no detectable acquired immune response in their host
- Prion diseases are usually rapidly progressive and always fatal
- characteristic lesion- spongiform degeneration with activation and proliferation of astrocytes and microglia in brain and spinal cord
- extremely resistant to inactivation by heating, chemicals and ultraviolet & γ -irradiation
- Prions are stable at a wide pH range

Properties of Prions

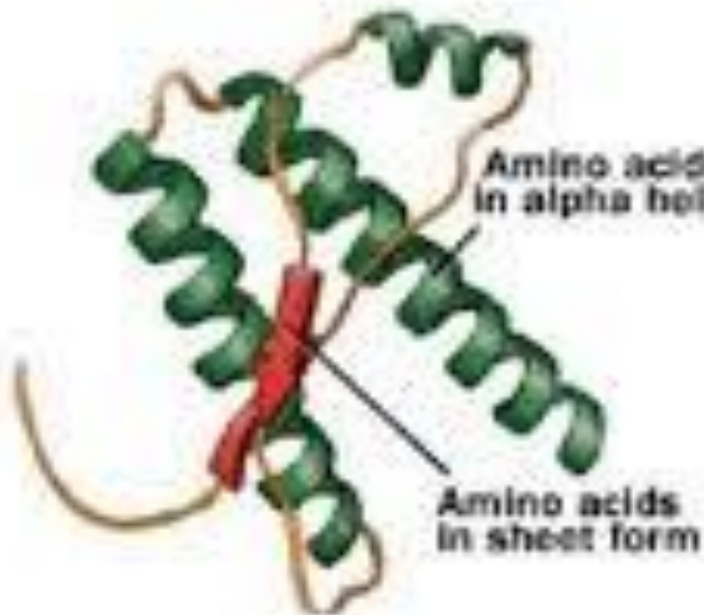
- Treatment of prions with alcohols and aldehydes that fix proteins may help to stabilize rather than inactivate these agents
- Autoclaving at temp. 132°C recommended, it does not ensure prion inactivation
- High concentrations of sodium hypochlorite or hot solutions of sodium hydroxide may inactivate this thermostable agent

Prion Protein

- normal protein, called PrPC (normal cellular isoform of prion protein) ubiquitously expressed
- reaches particularly high levels in neurons and follicular dendritic cells
- abnormal isoform of the protein is called PrPSc
- In a prion-infected individual, only the conformation of PrPSc changes
- Protein size highly variable depending on the strain

Normal and scrapie prion protein

Normal



Diseased prion



- Abnormal folding of the prion proteins leads to brain damage and the characteristic signs and symptoms of the disease.
- Responsible for several neurodegenerative diseases in humans and animals
- ‘Prion theory’ proposes that they are derived from a native glycoprotein
- polymerize after proteinase-K digestion, forming helically wound amyloid fibrils visible by electron microscopy

Structure of Prions- 02 isoforms

Normal prion protein/native glycoprotein(PrP^c) (cellular prion protein)

- ✓ associated with the plasma membrane of many cell types particularly neurons and lymphocytes
- ✓ important role in cell signalling and cell adhesion
- ✓ PrP^c is composed of more alpha helices than beta sheets

Abnormally folded form (PrP^{sc}) (scrapie prion protein)

- ❖ disease causing prion
- ❖ have more beta sheets
- ❖ resistant to proteases
- ❖ accumulates in cytoplasmic vesicles particularly lysosomes

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Formation of PrP^{Sc} from PrP^C

- may be initiated following exposure to an external source of PrP^{Sc}, usually by ingestion
- Rarely, random spontaneous conversion of native PrP^C to PrP^{Sc}
- mutation in the **PrP^C gene** configurational change in prP^C

‘Species barrier’- The resistance of some species to infection by prions derived from another species is species barrier.

Prion diseases are distinguished by:

- ❖ long incubation periods
- ❖ characteristic spongiform changes associated with neuronal loss
- ❖ failure to induce inflammatory response

Transmissible spongiform encephalopathies include:

- Scrapie in sheep
- Bovine spongiform encephalopathy
- Feline spongiform encephalopathy
- Transmissible mink encephalopathy
- Kuru and Creutzfeldt-Jacob disease in humans

Bovine spongiform encephalopathy

- commonly known as **mad cow disease**
- Usual onset: 4–5 years after exposure
- Neurodegenerative disease of cattle, caused by prion protein.
- transmitted through consumption of BSE-contaminated meat and bone meal supplements in cattle feed.



Types: Classic, atypical

Classical BSE:

- occurs through the consumption of contaminated feed

Atypical BSE:

- refers to naturally and sporadically occurring forms
- believed to occur in all cattle populations at a very low rate
- have only been identified in older cattle

Symptoms

- Hyperesthesia with kicking during milking
- Reduced milk yield
- Abnormal behaviour, abnormal posture
- Weight loss
- Hind limb ataxia, trouble walking
- Later in the course of disease, cow unable to move
- The disease inevitably fatal after a clinical course ranging from 2 to 3 weeks to over a year

Diagnosis

- By histopathology (i.e. microscopic examination) of the medulla oblongata
- Immunohistochemical (IHC) techniques
- Western immunoblot
- **Prevention:**
 - ✓ Not allowing older animals to enter the food supply
 - ✓ Disallowing certain products in animal food

Scrapie

- Fatal, neurological disease of **adult sheep and goats**
- Occurs worldwide except in Australia and New Zealand
- Susceptibility of sheep to scrapie influenced by polymorphisms in the PrP gene (PRNP)

Potential modes for natural infection-

- ✓ Ingestion
- ✓ Entry through superficial abrasions
- ✓ Transmission from ewe to lamb



Pathogenesis and pathology

- Following natural infection, prpSc is usually first detected in tissues of the lymphoreticular system including spleen, palatine tonsil and retropharyngeal and mesenteric lymph nodes
- In lymph nodes, replication apparently occurs in follicular dendritic cells
- Following ingestion of prions, infection is initiated in gut lymphoid tissues
- Prions produced in these tissues then move to the central nervous system
- Neuronal and neuropil vacuolation and astrogliosis are associated with accumulation of prpSc in the CNS.

Clinical signs of Scrapie

- Long incubation period
- Incidence between 3-4 years of age
- Initially, affected animals have restlessness or nervousness, particularly after sudden noise or movement
- Fine tremors of the head and neck, in-coordination with a tendency to exhibit jerky movements are characteristic signs.

Clinical signs of Scrapie

- Pruritis may result in loss of wool
- In some affected sheep, a nibbling reflex can be elicited by scratching the back
- Progression of the disease leads to emaciation
- Death usually occurs within six months from onset of clinical signs.

Diagnosis

- Clinical signs and histopathological examination of CNS
- Characteristic microscopic changes-
 - neuronal vacuolation and degeneration
 - vacuolar change in neuropil and astrocytosis, particularly in the medulla
- No obvious inflammatory response is evident
- Immunohistochemical staining for PrPSc
- Immunoblotting to detect proteinase-K-resistant PrPSc
- Electron microscopy to detect scrapie-associated fibrils

Control

- Strict quarantine procedures
- Slaughter policies
- Control policy involving flock certification and movement restrictions
- Breeding scrapie-resistant sheep
(e.g. Suffolk sheep highly susceptible, Cheviots relatively resistant)

Thanks