

Prions

These infectious agents which (almost certainly) do not have a nucleic acid genome

ATYPICAL AGENTS

- SIMILAR TO VIRUSES
 - small
 - filterable
 - need host cells
 - no machinery for energy generation of protein synthesis
- DIFFERENT FROM VIRUSES
 - no detectable virions in infected tissues
 - no detectable virions in purified infectious material
 - if nucleic acid is present, very small
 - very resistant

Figure 1

It seems that a protein alone is the infectious agent and has been called a prion

purified infectious material

- protein present
- proteases inactivate
- nucleic acid controversial

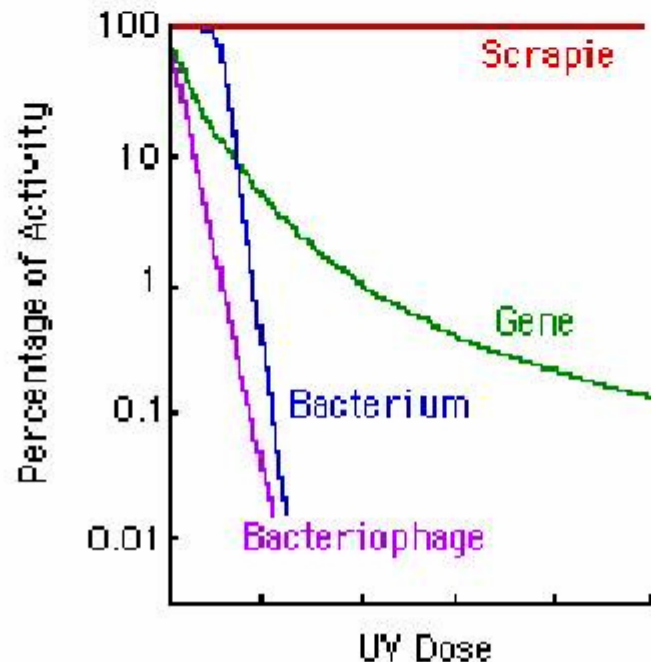
A prion has been defined as "small proteinaceous infectious particles which resist inactivation by procedures that modify nucleic acids"

- RESISTANT TO OR ONLY PARTIALLY INACTIVATED BY:
 - formaldehyde
 - ethanol
 - glutaraldehyde
 - ultraviolet and ionizing irradiation
 - non-ionic detergents

Figure 3

- **INACTIVATED BY:**
 - autoclaving (121C for one hour) (> standard)
 - 5% sodium hypochlorite
 - sodium hydroxide
 - proteases, urea, other protein denaturants

The discovery that proteins alone can transmit an infectious disease has come as a considerable surprise to the scientific community.



Prion diseases are often called spongiform encephalopathies because of the post mortem appearance of the brain with large vacuoles in the cortex and cerebellum.

Probably most mammalian species develop these diseases. Specific examples include

- Scrapie: sheep
- TME (transmissible mink encephalopathy): mink
- CWD (chronic wasting disease): muledeer, elk
- BSE (bovine spongiform encephalopathy): cows

Humans are also susceptible to several prion diseases:

- CJD: Creutzfeld-Jacob Disease
- GSS: Gerstmann-Straussler-Scheinker syndrome
- FFI: Fatal familial Insomnia
- Kuru
- Alpers Syndrome

OTHER HUMAN PRION DISEASES

- Gerstmann-Sträussler-Scheinker syndrome (GSS) (familial)
 - motor
- **new variant CJD (nvCJD, vCJD)**
 - psychiatric
- **fatal familial insomnia (FFI)**
 - circadian rhythm problems

The incidence of sporadic CJD is about 1 per million per year GSS occurs at about 2% of the rate of CJD. It is estimated that 1 in 10,000 people are infected with CJD at the time of death. These figures are likely to be underestimates since prion diseases may be misdiagnosed as other neurological disorders.

PRION DISEASE

- CNS
- LOSS MOTOR CONTROL
- DEMENTIA
- PARALYSIS WASTING
- DEATH, FOLLOWING PNEUMONIA
- LONG INCUBATION
- SLOW COURSE OF DISEASE
- SPONGIFORM ENCEPHALOPATHY
- VACUOLATION OF NEURONS
- RARE IN MAN

IMMUNE RESPONSE

- no inflammatory response
- no interferon induction
- no anti-body response
- no cell-mediated response

The diseases are characterised by loss of motor control, dementia, paralysis wasting and eventually death, typically following pneumonia

Fatal Familial Insomnia presents with an untreatable insomnia and dysautonomia (dysfunction of the autonomic nervous system). Details of pathogenesis are largely unknown.

Visible end results at post-mortem are non-inflammatory lesions, vacuoles, amyloid protein deposits and astrogliosis (scarring of astrocytes).

GSS is distinct from CJD, it occurs typically in the 4th-5th decade, characterized by cerebellar ataxia and concomitant motor problems, dementia less common and disease course lasts several years to death. (Originally thought to be familial, but now known to occur sporadically as well).

CJD typically occurs a decade later has cerebral involvement so dementia is more common and patient seldom survives a year (originally thought to be sporadic, but now known to be familial as well)

SCRAPIE

- sheep
- loss of muscular control
- wasting
- glial proliferation
- vacuolation of neurons
- amyloid plaques
- abnormal properties infectious material



Transmission in sheep:

1. Infection of pasture with placental tissue carrying the agent followed by ingestion, or direct sheep-lamb transmission.
2. Genetic disorder and not an infectious transmission. Should be able to get rid of disease by selective breeding.

Humans might be infected by prions in two ways:

1. Acquired infection (diet or medical procedures; consistent with infectious agent.
2. Apparent hereditary mendelian transmission where it is an autosomal dominant trait. (not consistent with infectious agent)

KURU

- tremors, ataxia, weakness
- dementia, death
- amyloid plaques
- spongiform changes

Brought prions to prominence in 1950s.

Found in isolated tribes in New Guinea

Route of infection: eating brain tissue of dead relatives

Several lines of evidence support protein only model of infection

1. Nucleic acid is not necessary for infectivity
2. PrP^{sc} is associated with scrapie infectivity
3. Susceptibility of a host to prion infection is co-determined by the prion inoculum and the PrP gene
4. Mutated gene can cause susceptibility to disease without apparent infection
5. Crucial experiment:
 - mice carrying mutated transgene spontaneously develop scrapie-like disease
 - mice lacking PrP^c gene develop normally and are resistant of scrapie-like disease