

Lecture Outline**Prions****Feb 28, 2001****I. Prions**

Prions are defined as proteinaceous infectious particles that lack nucleic acid. (protein/virion= prion). Prions cause a wide range of neurologic diseases in sheep, cows, and humans and were identified by Stanley Prusiner at UCSF in 1981.

Normal cellular prion protein = PrP^c
Abnormal disease causing isoform = PrP^{Sc}

PrP^c is found throughout the body but primarily expressed in nervous tissue and appears to have a role in synaptic function.

Many different possible mutations in the amino acid sequence of PrP^c can result in mutant PrP^{Sc}.

PrP^{Sc} undergoes different protein folding and conformation changes, which alters its protein properties.

PrP^{Sc} gets deposited in brain tissue causes neurologic damage which can lead to dementia and death.

Human prion diseases can present as genetic or infectious disorders.

Genetic: Mutations in PrP gene which lead to aberrant protein form.

Familial **Cruetzfeld-Jakob disease (CJD)** is thought to be germline genetic disease.

II. Infectious prion diseases.

Transmissible Spongiform Encephalopathies (TSEs) are a subset of the prion diseases which are acquired by infection but the exact transmission of the infectious agent or prion is unclear.

Transmission occurs primarily through eating of contaminated brain tissue.

How does a protein transmit disease?

PrP^{Sc} along with another protein appears to alter the protein structure of the native PrP to produce more of the mutant PrP^{Sc}.

III. Experimental Data on TSE prion diseases

Human: Slow growing takes many years before disease onset. Original human disease called **Kuru**. Disease of cannibals in New Guinea. Hard to isolate and identify infectious agent.

Also transmission through transplanted corneas, injections of Human growth hormone (HGH)

Mice: Mouse model developed by injecting infected tissue from sheep or human into mice.

Mice develop similar neurologic disease and have little immune response to the mutated self protein.

IV. "Madcow" disease same as **bovine spongiform encephalopathy (BSE)**.

1984-2000 200,000 diseased cattle died. Over 4 million with potential infection were slaughtered. Primarily in United Kingdom but recently found in European cattle.

So far none detected in U.S. cattle.

1994 First infection in humans. 87 cases in humans.

A. Source of BSE prions.

Disease thought to come from Scrapie in Sheep. (Scrapie is very common in sheep)

Presumably BSE is a cattle-adapted form of scrapie PrP^{Sc}. The agricultural practice of preparing tissue from rendering discarded animal carcasses (sheep, cattle, pigs, chickens) into protein rich feed called meat and bone meal (MBM). Dairy cows were fed MBM which included infected sheep brain tissue. BSE spread among cattle as undetected BSE infected cattle carcasses were used to prepare MBM.

It is thought that changes in the rendering process to prepare the MBM that occurred in late 1970s may have inadvertently allowed more PrP^{Sc} to survive the MBM preparation process.

B. Efforts to control BSE epidemic.

Laws to stop using feed derived from animal carcasses.

C. Variant Cruetzfeld-Jakob Disease (vCJD) in humans from BSE?

Ten year lag time between diseases. Humans were infected by nervous tissue contaminated meat products. e.g. meat with nervous tissue still attached, T-bone steaks.

Human genotype of PrP^c may play a role in genetic susceptibility of humans to this vCJD. .