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Prions – small infectious particles

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A prion is thought to be an infectious agent that according to current scientific consensus, is comprised entirely of a propagated, misfolded protein. The misfolded form of the prion protein has been implicated in a number of diseases in variety of mammals; include bovine spongiform encephalopathy (BSE, that is "Mad cow disease") in cattle and Creutzfeldt Jacob disease (CDJ in humans). All hypothesized prion diseases affect the structure of the brain or other neural tissue and all are currently untreatable and are always fatal. In general usage, prion refers to the theoretical unit of infection. Scientifically speaking, PrP^c refers to the endogenous prion protein, which is found in multitude of tissues, while PrP^c refers to the misfolded form of PrP^c, and is responsible for the formation of amyloid plaques that lead to neurodeaeneration. Prions are hypothesized to infect and propagate by refolding abnormally into a structure, which is able to convert normal molecules of the protein into the abnormally structured form. All known prions induce the formation of an amyloid fold, in which the protein polymerizes into an aggregate consisting of tightly packed beta-sheets. This altered structure is extremely stable and accumulates in infected tissue, causing cell death and tissue damage. This stability means that prions are resistant to denaturation by chemical and physical agents, making disposal and containment of these particles difficult. Proteins showing prion-type behavior are also found in some fungi and this has been quite important in helping to understand mammalian prions. However, fungal prions don't appear to cause disease in their hosts and may even confer an evolutionary advantage through a form of protein-based inheritance. The word prion is a portmanteau developed by combining the first two syllables of the words proteinacious and infectious (-on by analogy to virion).

Discovery:

The radiation biologist Tikvah Alper and the mathematician John Stanley Griffith developed the hypothesis during the 1960s that some transmissible spongiform encephalopathies are caused by an infectious agent consisting solely of proteins. This theory was developed to explain the discovery that mysterious infectious agent causing the diseases scrapie and CDJ resisted UV radiation (UV radiation causes direct DNA damage by exciting individual molecules in the DNA polymer, which causes errors to be introduced into base pair sequence). Francis Crick recognized the potential importance of the Griffith protein-only hypothesis for scrapie propagation in the second edition of his famous "Central dogma of molecular biology." Stanley B. Prusiner of the University of California, San Francisco announced in 1982 that his team had purified the hypothetical infectious prion, and that the infectious agent consisted mainly of a specific protein though they didn't manage to satisfactorily isolate the protein until 2 years after Prusiner's announcement. He coined the term "Prion" (NPW, 1997).

Structure:

Isoforms:

The protein that prions are made of is found throughout the body, even in healthy people and animals. However, the prion protein found in infectious material has a different folding pattern and is resistant to proteases, the enzymes in the body that can normally break down proteins. The normal form of the protein is called PrPc, while the infectious form of the protein is called PrP^{sc} – the c refers to 'cellular' or 'common' PrP, while the Sc refers to 'scrapie', a prion disease occuring in sheep. While PrP^c is structurally well defined, PrPsc is certainly polydisperse and defined at a relatively poor level. PrP can be induced to fold into other more-or-less well defined isoforms *in vitro*, and their relation-ship to the form(s) that are pathogenic *in vivo* is not yet clear.

PrP^c:

Normal protein found on the membrane of cells has 209 amino acids (in humans), one disulfide bond, a molecular weight of 35-36 KDa and a mainly alpha-helical structure. Many topological forms; one cell surface form anchored via glycolipid and two transmembrane forms. It binds copper (11) ions with high affinity. It readily is digested by proteinase K and can be liberated from the cell surface *in vitro* by the enzyme phosphoinositide phospholipase C (PI-PLC), which cleaves the

glycophosphatidylinositol (GPI) glycolipid anchor.

PrP^{sc}:

Infectious isoform of PrP^{c} is able to convert normal PrP^{c} proteins into the infectious isoform by changing their conformation. There is increased beta-sheet content in the diseased form of the molecule, replacing normal areas of alpha helix.

Function:

Precise function is unknown, but there is substantial evidence that it serves as Cu dependent antioxidant.

Prion disease:

Prions cause neurodegenerative disease by aggregating extracellularly within the central nervous system to form plaques known as amyloids, which disrupt the normal tissue structure. This disruption is characterized by "holes" in the tissue with resultant spongy architecture due to vacuole formation in neurons. Other histological changes include astrogliosis and absence of inflammatory reaction. While the incubation period for prion disease is generally quite long, once symptoms appear the disease progresses rapidly, leading to brain damage and death. Neurodegenerative symptoms can include convulsions, dementia, ataxia (balance and co-ordination disfunction), and behavioral or personality changes. All known prion diseases, collectively called transmissible spongiform encephlopathies (TSEs), are untreatable and fatal. However, a vaccine has been developed in mice that may provide insight into providing a vaccine in humans to resist prion infections. Following diseases are believed to be caused by prions.

In animals:

– Scrapie in sheep and goats.
– Bovine spongiform encephalopathy (BSE) in cattle.
– Transmissible mink encephalopathy (TME) in mink.
– Chronic wasting disease (CWD) in white-tailed deer, elk and mule deer.
– Feline spongiform encephalopathy in cats.
– Exotic ungulate encephalopathy (EUE) in nyala, oryx and greater kudu
– Spongiform encephalopathy in ostrich.

In humans:-

– CJD and its varieties; iatrogenic (iCJD), variant (vCJD), familial (fCJD) and sporadic (sCJD)
– Gerstmann – Straussler – Scheinker syndrome (GSS)
– Fatal familial insomnia (sFI)
– Kuru

Transmission:

Although the identified and general properties of prions are now well understood, the mechanism of prion infection and propagation remains mysterious.

Sterilization:

Infectious particles possessing nucleic acids are dependent upon it to direct their continued replication.

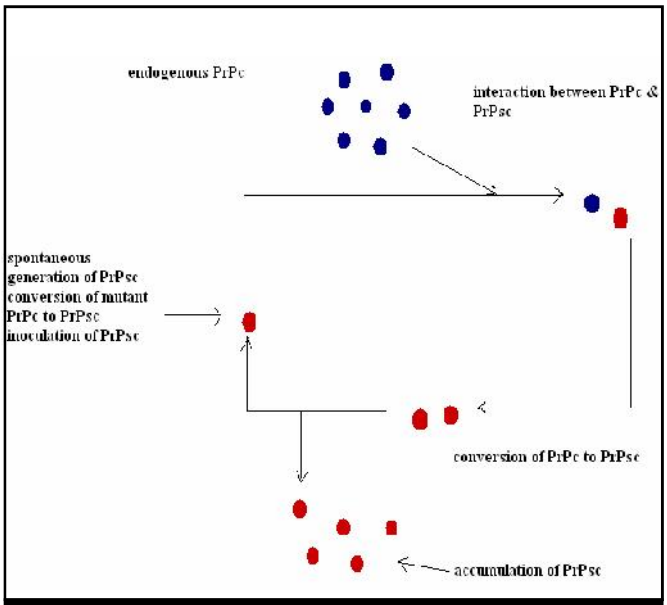

Fig. : Transmission of Prions

Prions, however, are infectious by their effect on normal versions of the protein. Therefore, sterilizing prions involve denaturation of protein to a state where the molecule is no longer able to induce the abnormal folding of normal proteins. However, prions are generally quiter to denaturation by proteases, heat, radiation and formalin treatments, although their infectivity can be reduced by such treatment.