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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