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PRION DISEASES

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Prion diseases are a group of diseases associated with impaired metabolism and accumulation in the cells of the central nervous system of prion proteins. All known prion diseases affect the structure of the brain or other neural tissue and all are currently untreatable and fatal. Prions are responsible for the transmissible spongiform encephalopathies in a variety of mammals. The human prion diseases include Creutzfeldt–Jakob disease, Gerstmann–Straussler–Scheinker disease, fatal familial insomnia and Kuru.

A conformational transition of normal cellular prion protein (PrP^{C}) to its pathogenic form (PrP^{Sc}) is believed to be a central event in the transmission of the devastating neurological diseases known as spongiform encephalopathies. These rare disorders can be acquired by infection, inheritance via mutations in the gene encoding for the prion protein, or occur spontaneously. Prions cause neurodegenerative disease by aggregating extracellularly within the central nervous system to form plaques known as amyloid, which disrupt the normal tissue structure. This disruption is characterized by "holes" in the tissue with resultant spongy architecture due to the vacuole formation in the neurons. Other histological changes include astrogliosis and the absence of an inflammatory reaction. While the incubation period for prion diseases is generally quite long, once symptoms appear the disease progresses rapidly, leading to brain damage and death. Neurodegenerative symptoms can include convulsions, dementia, ataxia and behavioral or personality changes. The abnormal PrP^{Sc} isoform has a different secondary and tertiary structure from PrP^{C}, but identical primary sequence. Although the exact 3D structure of PrP^{Sc} is not known, it has a higher proportion of β-sheet structure in place of the normal α-helix structure. Circular dichroism shows that normal PrP^{C} had 43% alpha helical and 3% beta sheet content, whilst PrP^{Sc} was only 30% alpha helix and 43% beta sheet.

The conversion of PrP^{C} to PrP^{Sc} conformation is the mechanism of transmission of fatal, neurodegenerative transmissible spongiform encephalopathies. Prion diseases are believed to be the result of the accumulation of PrP^{Sc}, but not of inhibiting the function of PrP^{C}. Due to small differences in PrP between different species it is unusual for a prion disease to be transmitted from one species to another. Prion diseases are usually rapidly progressive and always fatal. But the results of molecular-biological studies of the structure of prion proteins provided the basis to identify new directions for further approaches to the treatment of prion diseases.