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Prion: The Misfolded Protein

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Abstract: Prion is a cell surface protein expressed in a wide range of organs and tissues. This protein is mostly infamous for misfolding the similar proteins and causing prion diseases. Prion diseases are seen in humans as well as animals. These diseases are said to be fatal neurodegenerative diseases. Prions are made up of protein PrP which are also found in healthy humans and animals. In this review we will be understanding the concept of prion, its structure and the diseases caused due to it.

Index Terms **– Prion, misfolded protein, creutzfeldt – jakob disease, bovine spongiform encephalopathy, chronic wasting disease.**

I. INTRODUCTION

A protein is a naturally occurring molecule in the body. It is a complex and large molecule made up of amino acids and joined by peptide bonds. Prions are a type of protein which are not normal. They are misfolded proteins and they have the ability to affect the other normal proteins and make them misfolded proteins. The reason for misfolding of the protein is still unclear. Stanley Prusiner defined prion as a proteinaceous infectious particle in 1982. PrP^{SC} was the first prion to be discovered. It was a causative agent of scrapie disease (a transmissible neurodegenerative disease of sheep). The precursor of PrP^{SC}, the normally folded protein PrP^{C} was found later. The formation of hydrogen bonds between amino and carbonyl groups transforms PrP^{SC} into PrP^{C} [2, 4, 5].

II. WHAT IS A PRION?

Prions are misfolded proteins that can convert normal variant of the same protein into a misfolded protein. Due to this misfolding, there are a number of diseases known as prion diseases which are transmissible spongiform encephalopathies (TSEs) in sheep, chronic wasting disease (CWD) in deer, bovine spongiform encephalopathy (BSE) in cattle (commonly known as mad cow disease) and Creutzfeldt – Jakob disease (CJD) in humans but none of the diseases have an effective treatment and are mostly fatal. Prions cluster together to form amyloids which are present in the tissues and damage the tissues and cause cell death. Amyloids are clusters of protein. They are also one of the causes for diseases such as Alzheimer's disease and Parkinson's disease. Prions are pretty much stable proteins that is they don't get denatured by any chemical and physical agents [1, 10].

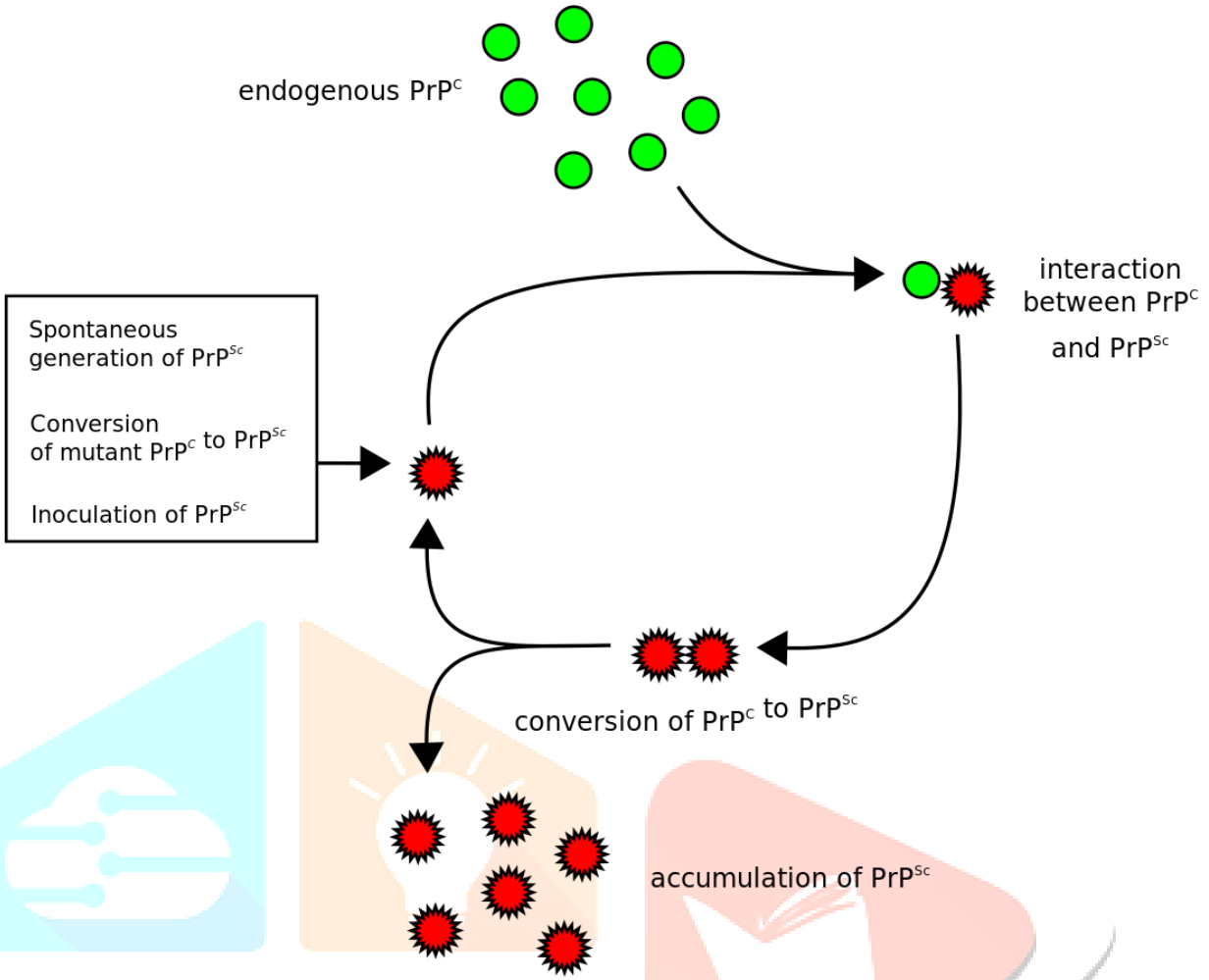

Figure 1 Mechanism of Prion Propagation

III. STRUCTURE OF PRION

The structure of prion protein (PrP^C) is classified into two domains which are N – terminal also known as disordered domain and a C – terminal also known as α-helical domain. The N – terminal has a positively charged region. It is vital for the endocytosis of prion. Here, a series of four octapeptide allow PrP^C to bind divalent metal cations such as Cu_2^+ and Zn_2^+. The C – terminal is comprised of three α – helices and two short β – strands. It is also the site of the post – translational modifications in PrP^C: that is, up to two N – glycans are added within the α – helical domain. A single disulphide bridge links helices 2 and 3 and a GPI anchor at the C – terminal attaches PrP^C to the outer surface of the plasma membrane [3, 7].

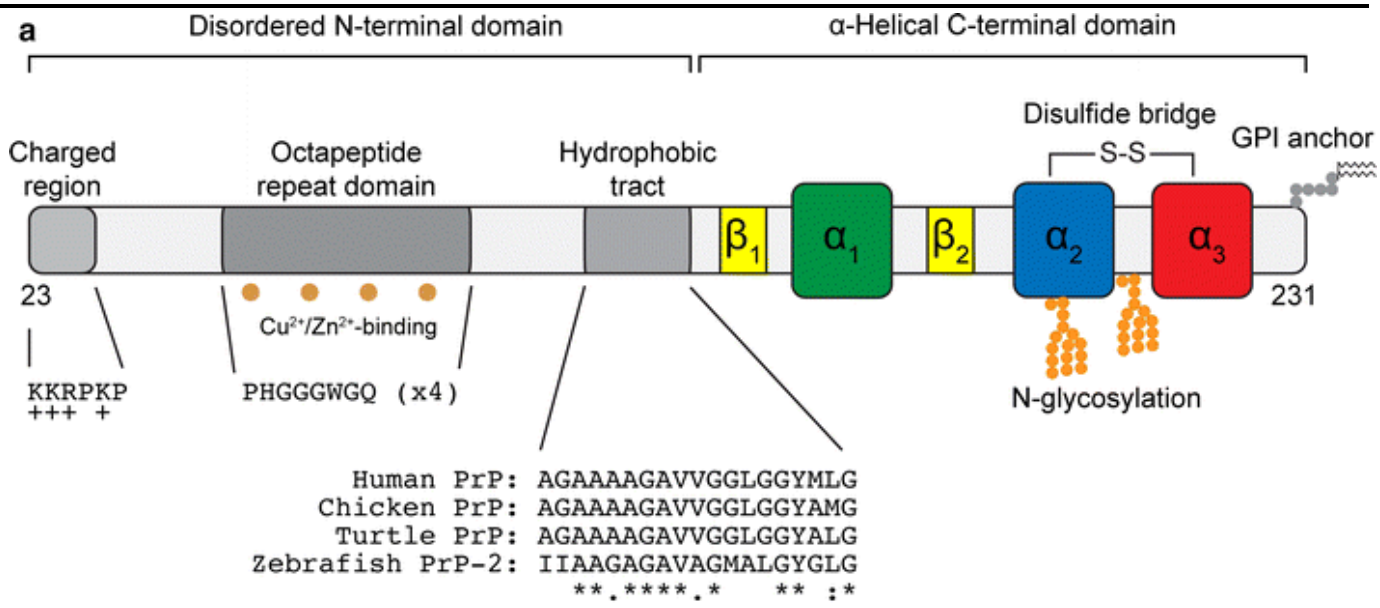

Figure 2 Structure of Prion Protein [3]

IV. DISEASES CAUSED DUE TO PRION

Prion diseases such as Creutzfeldt – Jakob disease (CJD) in humans, scrapie in sheep and bovine spongiform encephalopathy (BSE) in others are a few of the common ones. Human prion diseases can be classified into genetic, sporadic and acquired forms. All prion diseases are characterized by accumulation of PrP^{SC} in the central nervous system in the form of plaques or as synaptic deposits. Genetic PrDs (gPrDs) are all caused by mutations in the PRNP gene, which encodes PrP^{C}, and include genetic Creutzfeldt–Jakob disease (gCJD), fatal familial insomnia (FFI) and Gerstmann – Straeussler – Scheinker syndrome (GSS) [8, 9, 10].

The detection of misfolded prion protein is a complicated method due to the excess of normal cellular prion protein. Diagnosis of the nature of prion diseases, it's transmission and the danger of contracting the disease is done by studying the clinical symptoms followed by magnetic resonance imaging (Mri) and electroencephalography (eeG). Conventional methods of detecting diseases such as immunoblotting and enzyme – linked immunosorbent assay (ELISA) techniques are not efficient enough to detect the disease. Protein misfolding cyclic amplification (PMCa), the amyloid seeding assay and quaking – induced conversion (QuiC) are used to detect minute levels of prion proteins which cause infection in humans and animals. The real-time QuiC (rt – QuiC) assay now allows to detect Creutzfeldt – Jakob disease (CJD) in humans with 96% sensitivity and 100% specificity. The PMCa assay has been used for blood – based diagnosis of vCJD [6].

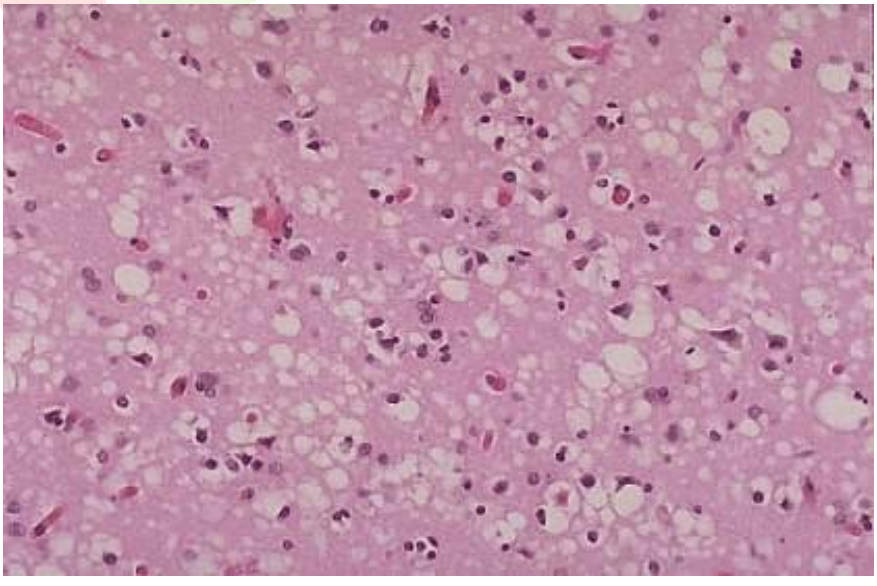

Figure 3 Sponge – like lesions in the brain tissue of a CJD patient

4.1 Creutzfeldt – Jakob disease (CJD)

CJD is a human prion disease and is a neurodegenerative disorder which is very progressive and generally leads to death within one year of onset of the disease. The symptoms mainly include rapid mental deterioration such as memory loss, personality changes, impaired thinking, blurred vision or blindness, insomnia, incoordination, difficulty speaking, difficulty swallowing and sudden, jerky movements. With the progress of the disease, the symptoms get worst. Creutzfeldt – Jakob disease is classified under a large group of human diseases known as transmissible spongiform encephalopathies (TSEs). The risk of developing CJD is low and it cannot spread through coughing, sneezing and touching.

CJD can be developed in three ways which are sporadically; that is many people with develop the disease for no apparent reason so it is known as spontaneous CJD or sporadic CJD. Second is by inheritance; it can be transferred genetically if there is a family history of the disease. Lastly by contamination; when people are exposed to infected human tissue during a medical procedure, they can develop the disease. A group of people had developed the disease from eating beef infected with mad cow disease (bovine spongiform encephalopathy, BSE), this was known as Variant CJD. In 1996, variant Creutzfeldt – Jakob disease (vCJD) was discovered in the United Kingdom. There is no particular preventive measure for this disease [11].

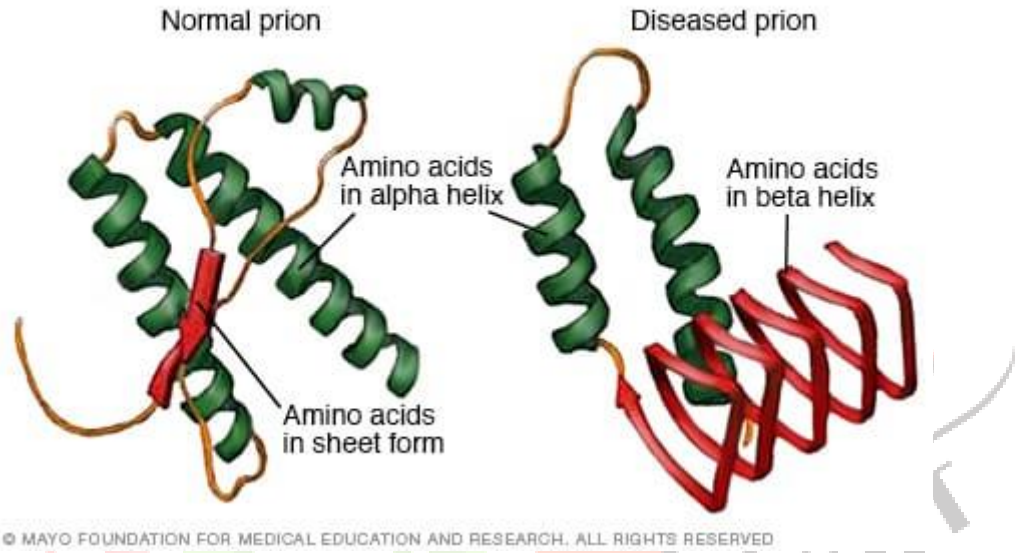

Figure 4 Normal Prion (left) and Diseased (affected with CJD) Prion (right)

4.2 Bovine Spongiform Encephalopathy (BSE)

Bovine Spongiform Encephalopathy (BSE) is a very progressive neurological disease of cattle that damages the central nervous system. It is also known as the mad cow disease. Researchers have found that it first occurred in 1970's. It is said that cows were fed with meat and bone meal which had infected BSE particles [11].

4.3 Chronic Wasting Disease (CWD)

Chronic Wasting Disease (CWD) is another prion disease that affects deer, elk, reindeer, sika deer and moose irrespective of age. It is seen mostly in North America, Norway and South Korea. Similar to CJD, CWD does not have particular treatment. After an animal has contracted the disease, the symptoms are noticeable after a year. The symptoms include weight loss, stumbling, listlessness and other neurologic symptoms [11].

V. CONCLUSION

Prion protein is a misfolded protein which causes a number of diseases. More research needs to be done to understand the cause of misfolding and how to reduce the misfolding in order to reduce the spread of disease. There should be more studies to find treatments or vaccines for prion diseases [4].

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