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INFLUENCE OF INFECTIOUS PRION PROTEINS ON DIFFERENT NEURODEGENERATIVE DISORDERS AND THEIR POTENTIAL TRANSMISSION TO HUMAN BEINGS FROM DIFFERENT SOURCES

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ABSTRACT: Prion proteins are cellular proteins (PrP^C), involved in neuroprotection. These are converted into abnormal scrapie isoforms (PrP^{Sc}). The gene (PRNP) encoding this protein is localized on the shorter arm of the chromosome number 20. Accumulation of the scrapie isoforms in the pre-synaptic terminals can cause prion diseases, resulting in neuronal loss and malfunction in impulse conduction. These infective scrapie isoforms can transmit from human to human, from environment to human and also from other infected animals. These may lead to **transmissible spongiform encephalopathies** in human beings**.** Known human prion diseases are Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker (GSS) disease, Kuru and fatal familial insomnia (FFI). The threat regarding these infective proteins is they can persist in the environment for a longer time period. These can bind to soil. These can transmit through surgical metal instruments, blood, swab, urine or faecal matter. These enter human body mainly through surgical infection, coming upon contact with infected animals or their meat, and from contaminated environment.
Keywords: Prion proteins; Scrapie isoforms; Prion diseases; Neurodegenerative disorders; Transmissible spongiform encephalopathies.

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INTRODUCTION

Prion proteins are genomic products, encoded by chromosomal genes. Contagious forms of these proteins are formed during the post-translational modifications and are said to be the only group of pathogens without genome [87]. This discrete feature differentiates prions from viruses [87, 12]. Neither viral particles nor disease-specific nucleic acids are isolated from these agents till date [79, 85]. For the transmission of prion disease a hydrophobic protein contained in the scrapie agent is critical [82]. Prions are "small proteinaceous infectious particles that resist inactivation by procedures which modify nucleic acids" [83]. These particles are conformed to be proteins as they are able to resist radiation, nuclease activity, and more importantly they can be modified by protein modifying procedures [6]. Later it came to knowledge that, prions are glycoproteins [19, 40, 75]. Prion proteins are responsible for transmission and pathogenesis of prion diseases [86]. Prion diseases are otherwise called transmissible spongiform encephalopathies (TSEs). These are a group of neurodegenerative disorders affecting many species, including human beings [88]. These diseases have a unique infectious agent i.e. PrP^{Sc}, a scrapie cellular isoform of a normal cellular protein, PrP^C [83, 3, 5]. In TSEs inflammatory sensations and degenerative qualities are observed and therefore they are often called autoimmune disorders [100].

Prion proteins

PrP^C is the normal product of the prion protein gene i.e. PRNP. This gene is present on the shorter arm of the 20th chromosome [62, 92, 102]. A precursor protein is proteolysed in the Endoplasmic Reticulum and Golgi to produce the mature version of the PrP^C [103]. A terminal sequence of protease resistant, PrP^{Sc} which is about 27–30 kDa, is designated as PrP27-30 [84]. PrP27-30 is derived from PrP^{Sc}, a molecule of about 33–35 kDa [75]. A small, protease-resistant molecule of around 142 amino acids is formed by restricted proteolysis of PrP^{Sc} and designated as PrP27-30 that polymerizes into amyloid [71]. Protease resistant prion isoform ($PrP^{res/Sc}$) can be produced from normal PrP^C that can infect a healthy host [57]. In mammals prion protein is highly conserved [114]. PrP is present in the majority of the tissues in adults [69]. But these proteins are highly expressed in CNS, especially in synaptic membranes and in cells of the immune system [41]. PrP^C is confined to synaptic boutons [74]. PrP^C has neuroprotective effects and autoimmunity [113]. Pattern of Protein glycosylation is different in different cell types. Hence different PrP^{Sc} glycosylation pattern may discriminate several prion strains [34]. These proteins have the capability to replicate themselves [48].

Conformation of Prion protein (PrP)

PrP^{Sc} and PrP^C are identical in their composition of amino acid sequences but differ in the three-dimensional conformation. After posttranslational modifications PrP^C is converted into PrP^{Sc} [21, 28]. PrP^C is rich in α-helixes and lacks β-sheet whereas PrP^{Sc} lacks α -helixes and has much more β-sheet [77]. Scrapie prions are the result of abnormal conformation of normal prion proteins, hence these may be called infectious proteins [77, 104, 109]. It is believed that conversion of PrP^C into PrP^{Sc} may be mediated by antibodies acting against PrP^{Sc} itself [117, 63]. Optimal pH for normal prion proteins is 7.2 but if the pH comes down, the normal PrP^C converts into PrP^{Sc} [107]. Isoform of normal cellular prion proteins can resist extreme conditions [108]. Conversion of PrP^C into PrP^{Sc} is not responsible for the disease in some cases [30].

Animal Prion diseases

Prion diseases are a group of neurodegenerative fatal disorders of Central Nervous System. Amassing of protease resistant PrP^{Sc} in affected areas of the brain is the fundamental attribute of these disorders [88].Prion diseases or TSEs affect a variety of mammals. These include bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep and goats, chronic wasting disease (CWD) in cervids (e.g., deer and elk etc.), transmissible mink encephalopathy (TME) in farmed mink, and Creutzfeldt-Jakob disease (CJD) and kuru in human beings. In sheep scrapie is a transmissible neurodegenerative disorder [36]. Pathological features of kuru and scrapie are almost equal [50].Basic mechanism of these disorders is the accumulation of PrP^{Sc} which is derived from the host PrP^C [89]. Presence of PrP amyloid plaques is clearly diagnostic of a prion disease [38]. These affect cattle, deer and human beings [88, 4]. Role of PrP^C is vital in pathogenesis of these diseases. Mice those are devoid of PrP^C can resist prion infections [26]. In recent years prions have also been identified in Bacteria [116, 39]. There are some chronic symptoms observed in prion diseases, like neuronal loss, gliosis, malfunction in synaptic transmission etc. [31, 49]. Heavy accumulation of PrP^{Sc} in synapse terminals causes synaptic disorganization and loss [58, 55]. The affected animals exert prion in their external secretions like urine [47], saliva [70, 67], milk [66], and faecal matter [93].

Human transmissible spongiform encephalopathies (TSE)

Known human prion diseases are Creutzfeldt–Jakob disease (CJD), Gerstmann– Sträussler–Scheinker (GSS) disease, Kuru and fatal familial insomnia (FFI) [90, 20, 96]. Rare cases of CJD and all cases of GSS and FFI are associated with mutations in human prion protein gene PRNP [96].Most frequent human TSE is Creutzfeldt-Jakob disease [96]. It is of four types, sporadic, familial, iatrogenic, and variant (sCJD, fCJD, iCJD, and vCJD). Among these about 1% of cases represent vCJD, 85 to 90% are sCJD, and 10% are fCJD [29]. But according to another study occurrence of sCJD is about 0·4–1·8 cases per 1 million people worldwide [22]. The fCJD are inherited as autosomal dominant traits, and cosegregate with mutations in the gene (PRNP), encoding prion protein [1]. In 1970s, person-to-person transmission of iCJD agent was reported [24].Bovine spongiform encephalopathy (BSE) prions can be transmitted to human beings and can cause vCJD [2, 53, 25, 10]. Different phenotypes of CJD are controlled by several types of human PrP^{Sc} [34, 78]. Fatal clinical signs are observed in human FFI but the levels of PrP^{Sc} are negligible [32, 72]; in certain occasions these can be transmitted to vulnerable animals, indicating the existence of infectious prions [33]. In vCJD, PrP^{Sc} is constantly produced in the lymphoreticular system [54] as considerable level of PrP^C is produced by lymphocytes [27]. Classical CJD may be transmitted from human to human through neurosurgical instruments [18] or by other surgical procedures [35]. Prions can adhere easily to metal surfaces and can be transmitted [118]. Iatrogenic CJD in humans can be resulted from the use of pituitary-derived hormone treatments, duramater grafts, corneal grafts [24] and also from blood transfusions [111]. After identification of the mechanism of transmission of iCJD prions, iCJD is declining but it may arise in future as the incubation period of these diseases is long [15].

Transmission of CWD prions to Human beings

In several possible ways CWD prions can be transmitted to Human beings. CWD prions may transmit through oral or nasal routes [51]. CWD prions can be shed in urine, faeces, saliva, blood, antler velvet and appear throughout host tissues including CNS [91, 46]. People those consume venison or come in contact with contaminated environment are exposed to CWD prions [95]. In USA, CJD cases with suspected CWD transmission have been reported [13, 14]. Scratching of diseased sheep and goats is one of the primary routes of transmission [59]. "Species barrier" is an obstacle in inter-specific CWD prion transmission, as prion strains are different in different species due to the difference in their amino acid sequences [16, 17]. These transmissible agents can adapt to any susceptible host species. But they become more virulent with repeated transmissions [8]. Species barrier in inter-specific prion transmission between human PrP and CWD prions is stronger than the species barrier in between human PrP and the BSE prion [94]. Transmissibility depends upon the three dimensional molecular shape of PrP^{C} and PrP^{Sc} and the molecular mechanism that converts PrP^{C} into PrP^{Sc} determines the strength of the species barrier for inter-specific transmission [61]. Intra-specific and inter-specific transmission of CWD prions may weaken the species barrier for transmission to humans [8]. Due to extensive exposure some CWD prions are being rigorously transmissible to human [9]. CWD is spreading geographically [110].

Transmission of prions from Environment to Human beings

Environmental exposure may play vital role in human disease transmission [44, 68, 37, 59, 52]. Prions may come into the environment through decaying carcasses, placenta, saliva, faeces, and urine [73, 46]. Soil particles have high affinity to bind to prions [101, 11] and prions enter into ruminants by ingestion of soil bound prions. Infection capability of soil bound prions last for a prolonged time period [23, 97]. It has been reported that soil bound prions have increased infectivity [56]. Several ecological vectors for the transmission of these diseases are scavengers [112], insects [115], and plants [81] and inorganic substances such as wood, plastic, and metals [118]. Susceptible organisms coming exposed to these vectors carrying the infectious proteins get infected and suffer from neurodegenerative disorders. These vectors are impossible to be identified. Hence these can spread prion diseases.

Treatment measures

Misfolded protein aggregation may lead to neurodegenerative diseases like Prion diseases, Alzheimer's disease, Parkinson's disease [99, 43, 98, 42]. There are not sufficient amounts of evidences representing successful prevention of protein misprocessing [76]. Chemical compounds designated as "dendrimers" are capable of eliminating prions from cells effectively [106]. Administration of certain drugs may hold-up the commencement of these disorders in animals [80]. Quinacrine has the capability to restrain PrP^{Sc} build up in human cells [60]. It is used comprehensively in human CJD treatment because of its ability to infiltrate the blood-brain barrier [64]. Quinacrine reduces the de novo synthesis of PrP^{Sc} [7]. In tauopathies, protein accumulation is not necessary because over-expression of tau proteins can hamper axonal transport [105, 45]. In this aspect PrP^{Sc}, responsible for prion diseases are different from other neurotoxic species [65].

CONCLUSION

Prion proteins are cellular proteins, having harmful effects after abnormal mutations. Diseases caused by scrapie isoforms of prion proteins are undetectable. It is the most dangerous aspect of these diseases. There is not any specific treatment measure or any detection methods for these fatal disorders. When we observe the symptoms of these disorders, we get to know that the patient is undergoing these disorders. Hence more research is needed to get rid of these disorders.

Conflict of Interest; The authors declare that they have no conflict of interest.

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