

Free essay on human prion proteins

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Prions are infectious proteins that are usually linked with the occurrence of neurodegenerative disorders in humans as well as many other mammals. They belong to the class of misfolded proteins and are the causative agents for the different transmissible diseases, mainly encephalopathy that can be defined by the changes in the anatomy accompanied by Pathophysiological origin that follow Mendelian genetics. The main characterization of the disease is the aggregation of proteins in the neurological system leading to degenerative brain diseases that are fatal and are incurable at present. Murray et al. (2004, p. 37) have stressed that the transmissible neurodegenerative diseases or the prion diseases are associated with spongiform changes, astrocytic gliomas and neuronal loss resulting from the deposition of insoluble protein aggregates in the neural cells. Nucleic acid has not been associated with this infectious agent and the improper protein conformation is the leading cause for these diseases. The main diseases that occur in humans associated with these proteins are Creutzfeldt-Jakob disease, Kuru, etc. The prion diseases are transmitted through proteins without any DNA or RNA involvement and are infectious, genetic or sporadic disorders. As they result from the misfolding of the proteins leading to alteration in the protein conformation, and thus physical properties of the proteins. The Human prion related protein is PrP, which is a glycoprotein encoded in the short arm of chromosome 20 and the normal PrP is known as PrP^c that is transformed to PrP^{sc} due to the transformation in the protein conformation. Murray et al. (2004, p. 37) have suggested that the PrP^{sc} is rich in β sheet with many hydrophobic aminoacyl side chains exposed to the solvent that helps in their strong association with one another, forming

protease-resistant aggregates. The presence of one pathologic prion can result in the conformational transformation of many times of PrP^{Sc} molecules thus helping in the transmission of the disease without the involvement of DNA or RNA. However, not much information is provided by them regarding the structure of the prion proteins and also the nature of the conformational changes that result due to the prion proteins.

According to Lodish et al. (2004, p. 73), the inheritance of the prion proteins follows Mendelian genetics. According to them the prion proteins containing α helices and their proteolytic fragments fold into alternative β sheet containing structures that form stable filaments by polymerization. Lodish et al. (2004, p. 97) have suggested that the structure of the complex of the prion proteins, in the initial stages of the formation of insoluble filaments, can be solved by crystallography of the subunits of the complex, that will result in the generation of a composite structure consisting of the x-ray derived subunit structures, fitted to the electron microscopy-derived model. However, the causes for the formation of β sheet from the α -helices of the prion proteins and the possibility of toxicity of the extracellular filament deposit or the soluble folded proteins remain to be seen.

Zuegg & Gready (2000, p 959-974) have analysed the effect of N-glycosylation in the prion proteins at the two glycosylation sites Asn181 and Asn197 by the comparison of the Molecular dynamics simulations of the HuPrP homology model with the result of the simulations of the HuPrP with the two N-glycans attached. The different possible orientations of the PrP with respect to the membrane defined by including in the model the oligosaccharide part of the GPI anchor bonded to the C-terminal Ser. The

simulations of the membrane model with the GPI anchor were combined with the results of the MD simulations of the HuPrP that is fully glycosylated for the identification of the possible distance between PrP and the membrane. The comparison of the dynamic and the structural behaviour of the glycans bound to the PrP with the results of the simulations of their free and solvated forms helped in the assessment of the restrictions on the flexibility of the glycans by the protein environment. From the experiments, they derived that N-glycosylations may be important for cell trafficking as well as the folding process of the proteins leading to their structural ability. Their experiments also suggested that N-glycans prevent the change of normal PrP to PrP^{Sc} and the correct folding of PrP is very essential for the correct processing as well as biosynthetic transport of the protein. However, the type of glycosidic linkages formed in the GPI-anchor model remained unidentified leading to the uncertainty in the model. Moreover, the simulation studies had very short simulation time that could not reveal the formation of any significant secondary structure.

Zahn et al. (2000) have found that the NMR structure of the recombinant human prion protein, hPrP (23-230) and two C-terminal fragments, hPrP (90-230) and hPrP (121-230) included a globular domain that extended from the residues 125-228, for which a detailed structure was obtained and an N-terminal flexibly disordered 'tail'. They cloned the recombinant human PrP polypeptides using E. coli expression plasmid that coded for the 17aa-N-terminal histidine tail containing an engineered thrombin cleavage site by applying some changes in the usual protocol like different temperature, etc. Their NMR studies (p. 146) showed the presence of a globular domain in the

intact recombinant human prion protein, hPrP (23-230) extending from residues 125-228, a flexibly extended N-terminal tail of residues 23-124 , and a short flexible chain end of residues 229-230, which is similar to the previously described structure of mPrP(23-231) and the characterization of shPrP.

According to Safar (2012), a centralized approach in the study of the neurodegenerative diseases is essential due to the presence of common aspects in the pathogenetic, diagnostic, and therapeutic aspects in the fundamental processes of the different neurodegenerative diseases. Hence, Translational Neurodegeneration Research (TNR) is needed for the in-depth understanding of the brain at the molecular, cellular, and neural circuit level and to translate new discoveries in the field into novel approaches for the treatment of these neurodegenerative diseases. According to him, there are four crucial areas in TNR- firstly, the understanding of the protein folding mechanism of neurodegeneration and the development of animal models to understand the pathophysiology that may be age-related to help in the development of diagnostic tools and therapeutics. Secondly, the understanding of the molecular mechanisms regarding the plasticity of the neural circuits help in the regeneration of the damaged and malfunctioning neural circuits. Thirdly, the development of Neuroimaging techniques along with the design and synthesis of new ligands for the misfolded proteins can help in the diagnostics. Fourthly, the development of new strategies can help in the reparative therapy of the neurodegenerative diseases like stem cell technology.

Linden et al. (2008) examined the physiological functions of PrPc at the

systemic, cellular and molecular level to understand the pathogenesis of TSEs (Transmissible Spongiform Encephalopathies). The study of the PrPc with different ligands has demonstrated their role in the modulation of several important cellular processes as well as cellular systems. They have been found to modulate: 1) Neural and immune systems, including memory and inflammatory reactions; 2) cell proliferation, differentiation, and sensitivity to apoptosis in both nervous and immune systems, as well as in various cell lines; 3) different signal transduction pathways including cAMP/protein kinase A, mitogen-activated protein kinase, phosphatidylinositol 3-kinase/Akt pathways, as well as soluble non-receptor tyrosine kinases; and 4) trafficking of PrPc among the domains of plasma membrane and along endocytic pathways with continuous, rapid recycling. Linden et al (2008) showed the role of the prion protein as a dynamic cell surface platform for the signalling modules assembly, due to which different signalling pathways across the transmembrane take place that are important for the physiology and behaviour. In this aspect, in-depth study is essential to elucidate the systemic effect of the prion proteins in the cellular processes and the different molecular and structural interactions associated with their functions.

Aguzzi, Sigurdson & Heikenwaelder (2008) have discussed the different molecular mechanisms that lead to neurodegeneration, the role of immunological system in the prion pathogenesis, and the existence of the various strains of prion that appear to have different tropisms and biochemical characteristics. According to them, the cellular prion protein (PrPc) is necessary for the development of the disease, which is shown by

the absence of susceptibility to prion disease in the prion knockout mouse. The accumulation of the aberrantly misfolded prion protein to form large amyloid plaques and fibrous structures in the central nervous system and lymphoid organs, leads to neurodegeneration. In spite of the identification of the different prion strains and understanding of the neurotoxic mechanisms of the prions, the molecular basis for neurodegenerative processes remains to be understood. The reasons behind the neurotoxicity induced by the prions and absence of immune toxicity, prion conversion mechanisms, maintenance and transmission of strain information, mechanisms of tropisms of prion strains, physiological functions of PrP^c, nature of prion agent, are some of the questions that need to be addressed by the prionologists.

Chen, Yadav & Surewicz (2010) have characterized the interaction between the synthetic A₄₂ oligomers and the recombinant human prion protein (PrP) using two biophysical techniques: site-directed spin labelling and surface Plasmon resonance. Their data indicated binding specific for a particular conformation adopted by the peptide in soluble oligomeric species, which was shown identical for the Met129 and Val129 polymorphic forms demonstrating the polymorphism of Prp codon 129 as a risk factor in the development of Alzheimer's disease (AD) due to factors unrelated to the interaction with A₄₂ oligomers. In addition to the identified 95-110 segment, the second region with crucial importance for interaction with A₄₂ oligomers is a cluster of basic residues at the extreme N terminus of PrP (residues 23-27). The two regions provide high affinity binding sites for the A₄₂ oligomers leading to loss of binding function. Thus, the interplay between the postulated protective and pathogenic roles of PrP in AD can be

explained by their studies that may help in the development of novel therapeutic strategies that target this interaction. However, the observation of the mediation of potential protective effect and toxic role in AD by the protein expressed by the same region of PrP is fascinating, suggesting for a balance of these effects controlled by additional cellular cofactors, which need to be found out.

According to Colby & Prusiner (2012), prions may not cause a disease, however they may function as regulators of cellular metabolism. The alignment of the sequences translated from more than 40 PrP genes exhibit high degree of conservation in the mammalian sequences that indicates the retention of PrP functions that may be important through evolution.

However, some variations have been indicated intra-species and inter-species that may affect the susceptibility of the prion infection. The therapeutic studies related to prion diseases may help in the development of drugs that may help in the treatment of various neurodegenerative disorders. The possible reduction or interruption in the formation of nascent prions with the application of treatment for a short duration of time may help in the cellular clearance mechanisms that overtake the synthesis of new prions. Hence, the application of therapeutics for a short period can be helpful instead of long-term treatment with the development of such drugs. Singh, Singh & Mohan (2010) have studied the physiological significance and pathological implications of PrP-metal interaction on the pathogenesis of prion disease. Neurotoxicity in the neurodegenerative disorders is mediated by the free radicals induced by the metals. The possible role of PrPc in metabolism of metals may explain the imbalance of metal metabolism in

case of the formation of PrP^{sc} due to loss of function of PrP^c leading to accumulation of PrP^{sc}. The gain of toxic function by PrP^{sc} due to sequestration of PrP^c-associated metals within the aggregates may result in the formation of redoxactive PrP^{sc} complexes. However, other physiological implications of the PrP^c-metal interaction are unclear. The pathological implications include the metal induced oxidative damage and in some cases, the conversion of PrP^c to PrP^{sc}-like form. The secretion of toxic chemokines by the microglia in response to the accumulation of PrP^{sc} leads to membrane damage. Prions have been found to be associated with the uptake of copper and iron with important role in the iron homeostasis. However, the roles of these redox-active metals in the generation of neurotoxicity and the underlying mechanisms involved are unclear. The infection caused by the prions are characterized by the conversion of PrP^cs, the host cellular proteins into the disease related forms, PrP^{sc} and this infection can be arrested in vivo by the anti-PrP monoclonal antibodies by passive immunization. Antonyuk et al. (2009) have analysed the ability of the monoclonal antibodies to cure the cells infected with prions based on its binding affinity for PrP^c instead of PrP^{sc}. They determined the crystal structure of human PrP, in its native conformation, bound to the Fab fragment of the monoclonal antibody ICSM 18 that has highest therapeutic efficacy, in vitro and in vivo. The polymorphic residue at position 129 and its role in genetic susceptibility and prion strain selection is explained by the mediating of protein-protein contact. The role of the polymorphic residue at 129 position, determines the folding of the proteins and the packing of the proteins within the prion particles as there is no effect of this variation on the

stability and physical properties of PrP^c. The heterozygosity of the residue also helps in the protection against the sporadic and acquired prion diseases in humans.

Belay and Schonberger (2005, p. 191) have analysed the risk related to human health due to the exogenous transmission of several prion related diseases in US that include the iatrogenic transmission of Creutzfeldt-Jakob disease (CJD), possible occurrence of variant CJD (vCJD), and the potential zoonotic transmission of chronic wasting disease (CWD). Although, the presence of a species barrier limits the cross-species transmission, the transmission of bovine spongiform encephalopathy to the humans can pose a serious health risk to the humans. The person-to-person transmission of some prion diseases such as vCJD via the blood products and the susceptibility of the vCJD transmission in the patient heterozygous at codon 129 have greater impact on the serious public human health risks. However, the prevention methods to avoid or lower the level of risk have not been elucidated.

Dobson (2001) has argued that the protein misfolding results in the formation of the neurodegenerative diseases. The rate of folding of the small proteins is dependent on the different interactions that are crucial for the formation of the native structure in vitro, hence are very fast compared to the larger proteins that take longer time for folding and formation of proper conformation. The folding and unfolding of the proteins are coupled to many signal transduction pathways within the body like trafficking of proteins, transport of proteins across the membranes, secretion of different proteins, cell cycle events, etc. Dobson has remarked that evolution helps in the

selection of some particular sequences that help in the proper folding and unfolding events of the proteins and the presence of any form of mutation causes the misfolding of the proteins. Toxicity of the aggregated proteins has been proved, that in turn suggests that the aggregated proteins not only result in the loss of function but also in toxicity of the cells.

The interaction of the prion protein with the amyloid- β ($A\beta$) oligomers is known, although the significance of this interaction was unclear. Nieznanski et al. (2012) proved that the prion protein and its N-terminal fragment inhibit the $A\beta$ 1-42 oligomers preventing the formation of the amyloid fibrils i. e. amyloidogenesis. Moreover, the prion protein prevents the formation of spherical oligomers that usually occur in the $A\beta$ fibrillogenesis, acting as a potent inhibitor of the $A\beta$ 1-42 toxicity as studied in the neuronal cell culture. The role of the recombinant prion protein and its N-terminal fragment in the prevention of aggregation of the $A\beta$ along with the inhibition of the formation of the amyloid fibrils at very low concentrations can open new gates for the therapeutics of Alzheimer's disease using its synthetic analogues/derivatives of these fragments.

Vincent (2010) has studied the different directions in the research related to the human prion proteins and its future comparing different reviews and journals. Human CJD is one of the most common prion related diseases that affects one per million every year. The genes associated with the prion diseases, the studies on the prions on the mouse models, etc have been compared using several published articles. It has been suggested that the in-depth understanding of the diseases is possible only by the characterization of the cellular PrP roles. However, the possibility of the role of viral cause in

the prevalence or spread of the disease can provide solution to a number of discrepancies observed in the study of the prions i. e. prion etiology.

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