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Transmissible Spongiform Encephalopathies & Prion Proteins: A Systematic Review

Anirban Poddar[1], T.N. Kundu[2], Manali Sinha Ray[3], Rituparna Maji[3*]

[1]Department of Biochemistry, Deben Mahato Government Medical College and Hospital, Purulia, India.
[2]Department of Neurology, R. G. Kar Medical College and Hospital, Kolkata, India.
[3]Department of Biochemistry, Calcutta National Medical College and Hospital,Kolkata, India.

Abstract

Prion proteins (PrPc) have been implicated as the causative agent of "Transmissible Spongiform Encephalopathies" (TSE). Apart from this devilish role, prions also have a bright facet of their own and their identity holds much more than just being a pathogenic entity. Role of prions as scaffolding proteins for ligand binding and signal transduction has been reported by several researchers. Role of prions in nerve impulse transmission at neuronal junctions, glyapse and gap junctions have been reported. Prion mediated regulation of calcium ion flux and redox status in turn regulates many major cellular functions. In this review we have focussed mainly on the physiological aspects of prion function apart from its pathological role in TSE. Role of prions in mediation of neuropathic pain, neuroinflammatory diseases and chronic headache has been reported by few researchers. In this review we have tried to correlate such effects of prions and also discuss various therapeutic targets for various diseases influenced by prions.

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Introduction

Recognition of prion diseases in early 1980's and subsequent research leading to the understanding of the molecular basis of same has revealed that the prion proteins are quiet an enigmatic protein themselves (Prusiner, 1982). They are known to cause a group of neurodegenerative disease in humans that are collectively referred to as Transmissible Spongiform Encephalopathies (TSE) (Prusiner, 1991). Some of these include Creuztfeldt Jakob disease, fatal familial insomnia, Gertstmann–Straussler–Scheinker syndrome, Kuru in humans. Similar diseases identified in cows, sheep and deer were named Bovine Spongiform Encephalopathy (BSE), Scrapie and Chronic Wasting Disease (CWD) respectively. The association of prions with TSE initially highlighted their negative role in cellular physiology. However, with subsequent research over the years, the role of prion proteins in normally functioning cells are becoming more apparent. Research during the past decade has provided us with substantial evidence regarding the role of prions in intracellular signal transduction,

CONTACT : RITUPARNA MAJI rituparnamaji123@gmail.com

epigenetic inheritance, long term potentiation of memories, thus leading us to believe that they work both in beneficial and harmful ways like a molecular switch (Sorgato, 2009). Prion proteins have been found in birds, reptiles, amphibians, fish (Premzl, 2004) with seven varieties of prions found in yeast alone (Goldschmidt, 2010). However interestingly enough the lower organisms such as insects, molluscs, protozoa (Aguzzi, 2008) seem to lack prions.

Structure of prions

The healthy prion protein is a 32- kDa protein with 253 amino acids that are coded by single copy of PRPN gene located on chromosome 207. The protein has regions that are highly conserved in all vertebrates (Taylor, 2006) (Insung, 2007).

Prions exist in at least 2 conformational isoforms:

1. PrPC: This is the healthy and fully functional prion protein existing in a healthy cell. Its structure is predominantly alpha helix rich (Zahn, 2000).
2. PrPSC: This is the isoform associated with prion diseases and it differs from the healthy isoform in being predominantly comprised of beta pleated sheet (Zahn, 2000).

The healthy isoform exists in two forms, the lipid bound form and the soluble or secretory form. The membrane bound form exists as a glycoprotein attached with a Glycosyl Phosphophadityl Ionositol (GPI) anchor bound to lipid rafts on the outer leaflet of the cell membrane (Colby, 2011). The soluble form on the other hand is not glycosylated.

The N-terminal end of the prion protein has an Intrinsically Disordered Component (IDC) extending from amino acid 23-121.It is referred to as intrinsically disordered as it does not have a permanent tertiary structure and is rather flexible (Jeon, 2013). The C-terminal end however assumes a permanent tertiary structure folded into 3 alpha helices and 2 short beta strands (Jeon, 2013). The diseased isoform has a similar primary structure as the healthy isoform, but differs from the healthy isoform in secondary structure as it has more beta sheets and less alpha helices in the C-terminal end. Another unique ability of the diseased isoform is its ability to form amyloid fibrils (Cobb, 2007). The diseased isoform is highly stable, resistant to proteolytic enzymes and selfreplicating (Prusiner, 1991).

The complete understanding of the various functions of prion proteins still remains elusive despite of aggressive research in past decade. Many of the elucidated and proposed roles of PrPc are associated with their location, i.e concentration in nervous tissue and localization in the membranes specifically in the lipid rafts. Various animal studies have pointed out that prions have an important role to play in:

1. Neuroprotection, neurogenesis and neuron polarisation (Linden, 2008)
2. Processing olfactory signals (Le Pichon, 2009)
3. Circadian rhythm (Huber, 1999)
4. Sleep patterns (Huber, 1999)
5. Memory (Criado, 2005)
6. Behaviour (Criado, 2005); (Nico, 2005).

Overexpression of PrPc has been shown to be associated with necrotising myopathy of skeletal muscle (Westgard, 2007) and other muscular disorders. PrPc has been found to be associated with neuroprotection and have been implicated to provide the muscles its required strength through the PPAR pathway (Filali, 2014). With these entire spectra of functions attributed to PrPc, the picture emerges is that of a protein with a versatility of function. Thus, pinning down the molecular basis of functions of PrPc poses a great challenge.

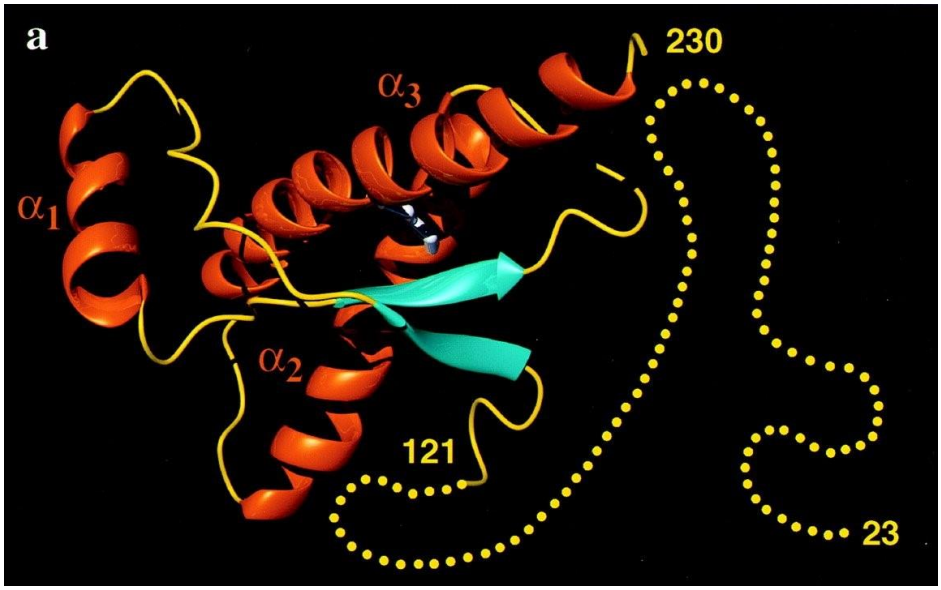

Figure 1. Structure of PrPc (Zahn, 2000) (Healthy Isoform of Prion Protein)

Prions and ligand binding

The IDC (Intrinsic Disordered Component) of the PrPc at the N terminal end is attributed to its promiscuous binding to multiple ligands (Linden, 2008); (Tompa, 2005). The binding of IDC to various ligands have been found to serve as a molecular switch for regulating signal transduction, gene expression and chaperone activity (Tompa, 2005). About 45 ligands have been identified that bind to the IDC of PrPc (Martins, 2010).

PrPC has been shown to bind to many molecules, including:

1. ECM proteins such as laminins (Graner, 2000) and vitronectin (Hajj, 2007), and glycosaminoglycans such as heparin and heparin sulfate (Warner, 2002).
2. Molecules on the outer leaf of the plasma membrane such as 37 kDa laminin receptor precursor (37LRP), 67 kDa laminin receptor (67LR) (Reiger, 1997), and ganglioside GM1 (Lewis, 2011).
3. Molecules on the inner surface of the plasma membrane such as Fyn kinase (Mouillet-Richard, 2000) and neuronal nitric oxide synthase (nNOS) (Keshet, 2000).
4. Intracellular membrane components such as glutamic acid decarboxylase (GAD)35, STI137, Bcl-2 37 and synaptophysin (Americo, 2007).
5. Transmembrane proteins including neural cell adhesion molecule (NCAM), 68 integrins, (Hajj, 2007) G-protein coupled serotonergic receptors (GPCR), (Mouillet-Richard, 2007) and G-protein receptors (Mouillet-Richard, 2007).
6. Transmembrane ion channels such as voltage-gated calcium channels (VGCC), (Whatley, 1995) (Fuhrrman, 2006) calcium-activated potassium channels (Herms, 2001), and two-pore potassium channel protein (TREK-1) (Azzalin, 2006).
7. Cytoskeleton proteins α-tubulin (Keshet, 2000), β-tubulin (Criado, 2005) (Neiznanski, 2005) and stathmin (Monnet, 2004).
8. Scaffolding proteins GRB2 (Spielhaupter, 2001), β-1 integrins (Loubet, 2012), synapsin (Spielhaupter, 2001) , Caveolin-1 (Mouillet-Richard, 2007), and protein complex 14-3-3 (Satoh, 2005), and
9. Chaperones and co-chaperones such as Hsp60(Edenhoffer, 1996), Hop/ STI1(Americo, 2007), αB-crystalline (Loubet, 2012), Rdj2 (Beck, 2006), and clusterin (Xu, 2008).

Prion diseases in humans: Known prion diseases in humans are:

1. Creutzfeldt Jakobs Disease,
2. Kuru,
3. Fatal Familial Insomnia,
4. Gerstmann Strausler Scheinker Disease.

Symptoms of prion diseases:

1. Behavioural changes such as loss of interest, aggression, personality changes.
2. Communication problems tend to occur. Speech initially gets slurred with eventully the patient becoming mute.
3. Memory and cognitive defects with a general decline in intellect.
4. Stiffness and rigidity of limbs followed by ataxia and gait disturbances.
5. Difficulty in swallowing is observed with progression of disease process.
6. Visual problems including double vision and difficulty in moving eyes to follow objects.
7. Seizures in later stages of the disease.

Mechanism of infectivity (The Seeding Hypothesis): The "Seeding Hypothesis" or "Protein Only Hypothesis" of prion disease transmission (Griffith, 1967) explains that the conversion of healthy prions to the diseased variety is an autocatalytic post translational conformational change that occurs when healthy prions (PrPc) interact with those of the diseased variety (PrPsc), where in the diseased prion acts as a template and hence recruits more healthy prions to aggregate into the beta diseased form (Halliday, 2014) .

Prion disease can be initiated by two mechanisms:

1. By introducing PrPsC protein, that recruits healthy prions to the diseased variety resulting in chain reaction that ultimately leads to the disease as in v-CJD and Kuru.
2. A mutation in the PRNP gene resulting in structurally defective prions which eventually leads to the disease as is the case with FFI, GSS.

When PrPc is synthesised in the endoplasmic reticulum, the correct folding of the same is assisted by a group of proteins called chaperones (HSP 110, HSP 60, αβ crystallin) (Carnini, 2010). Any misfolded protein is handled by the "Unfolded Protein Response (UPR)" of the cell, which might be either of three of these:

1. Chaperone assisted refolding of the protein.
2. Degradation of the unfolded protein by ubiquitin proteasome pathway if it cannot be correctly refolded by chaperones.
3. Isolation of the misfolded protein in cytoplasmic inclusion bodies called aggresoomes.

Interestingly enough it has been found that IDC components in a protein molecule make it more susceptible to misfolding (De Simone, 2012) (Qiao, 2013). Cellular mechanisms that maintain the homeostatsis of PrPc in a cell are as yet unknown, but the progression of the events to prion disease might definitely be seen as a failure in the quality control of the UPR of the cell.

Treatment

No specific treatment is available till date commercially. Treatment is mainly symptomatic which involves general therapy to prevent or reduce the symptoms as much as possible. Recent breakthrough in the treatment of Prion diseases include:

1. Phospholipase A2 inhibitors have been found to prevent prion replication.
2. Trimethylamine-N-Oxide (TMAO) has been found to stop the autocatalytic event of prion seeding. These drugs are presently under PHASE II trials.

Conclusion

The enigmatic proteins PRIONS evolved in higher vertebrates in due course of millions of years of evolution to perform specialized functions such as memory formation, neuron protection, synaptic plasticity, emotion response to name a few. Every tool wears out eventually and requires either appropriate corrective measures to rectify the same or its proper disposal. Similar is the case with the prions wherein an inappropriate folding or rather misfolding should be corrected by assisted folding through the chaperonin machinery which if not possible, a proper degradation and disposal through the Ubiquitin Proteasome Pathway should be ensured. When both these mechanisms fail, what results is neurodegene rative manifestations which we now know as the prion diseases. Thus, the cause of prion diseases might actually be attributed to a collective failure of the unfolded protein response of the cell and not just the prions.

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