Conformational Changes of Prion Protein and Nucleic Acid Arising from their Interaction and Relation of the Altered Structures in Causing Prion Disease

P.K. Nandi*

Infectiologie Animale et Santé Publique, Institut National de la Recherche Agronomique, 37380 Nouzilly, France

Abstract: Nucleic acids catalyse the conversion of α-helical prion protein to the β-structured protein oligomers and amyloids structurally similar to the infectious isoform of protein. Simultaneously, the prion protein, similar to gene regulating proteins, bends, unwinds and condenses nucleic acid. These properties might be related to the biological function and prion infection.

Key Words: Prion protein, nucleic acid, proin protein-nucleic acid interaction, conformational change, amyloids, DNA bending, DNA unwinding, DNA condensation.

INTRODUCTION

The naturally occurring fatal scrapie disease in sheep was first described as early as 1732 in France. The neuropathological and clinical similarities between scrapie and kuru, a disease of the Fore tribe of Papua New Guinea highlanders resulting from ritualistic cannibalism, were established in the late 1950s. Similarities in the pathology of the central nervous system (CNS) showed a link between scrapie, Kuru and a rare human neurodegenerative disease, the Creutzfeldt-Jakob disease (CJD) [1]. The disease is fatal and characterised by vacuolation of the CNS due to which the infected brain appears as sponge. Since the disease can be transmitted, it is also known as transmissible spongiform encephalopathy (TSE) [2]. Depending on their etiology, the disease can be divided into three categories viz. acquired (infectious), inherited and sporadic [3]. The disease is classified among amyloid disease since amyloid plucks are generally observed in the diseased brain. In both human and animal, spongiform degeneration causes neuronal loss and astrocytic proliferation [3]. The disease can be confirmed only after postmortem analysis of the brain or tonsil by immunoblotting and immunohistochemistry.

Conventional infectious agents viruses and bacteria cause infection and transmission of the diseases by specific nucleic acids present in their genomes. TSE has drawn considerable interest from late 1950s because the agent which caused and transmitted the disease was found to be strongly resistant to treatments which destroyed nucleic acids [4]. Instead, it is believed that the TSE is transmitted through an abnormal conformation of a cell-surface attached glycoprotein, termed 'prion' (acronym for proteinaceous infectious particle) [3, 5, 6]. TSE or prion disease has drawn tremendous attention in scientific, medical communities and governments in Europe, USA, Canada and Japan due to i) the appearance of a novel prion disease, bovine spongiform encephalopathy (BSE or mad cow disease termed so from the abnormal behaviour of the diseased animal) which reached epidemic proportion in the 1990s and ii) the evidence that variant Creutzfeldt-Jacob disease (vCJD) in humans is caused from the consumption of beef and related food products from the animal harbouring the BSE disease [3]. The United Kingdom has been the worst hit country by both these diseases. BSE was first diagnosed in the United Kingdom in 1986, peaked in 1992 and is believed to have resulted mostly from under processed scrapie-infected sheep carcasses (bone meal) used for cattle feed [7]. Although the vCJD in human appeared from prion infected cattle, sheep scrapie has not been reported to be transmitted to human [8]. Culling of BSE infected cattle in the late 1990s has tremendously reduced the number of BSE cases in the UK. vCJD patients identified so far could represent a distinct genetic subpopulation (homozygous for methionine at polymorphic codon 129 of the prion protein gene, where either methionine or valine may be encoded) with unusually short incubation periods for BSE agent [3, 9]. The total number of vCJD deaths till the end of 2007 is 161. The number of deaths peaked in the year 2000 in the UK (28 dead) have also decreased to a considerable extent (4 so far in 2007) (http://www.cjd.ed.ac.uk/figures.htm). However, it is uncertain whether the spread of the vCJDs has reached a plateau since the diseases have long incubation periods, and the development of the symptoms can take as long as fifty years or more. During such a long incubation period a carrier of prion infection is considered to be a potential risk to others through blood transfusion and contamination of surgical and medical instruments. It has been shown recently that prions that enter the body through a blood transfusion cause vCJD to develop faster compared to the disease arising in human through food chain [9].

THE INFECTIOUS AGENT

The detail molecular nature of prion still remains undefined. It is widely accepted that prion contains a certain population of multimeric, β-sheet rich, ProteinaseK resistant protein PrP^{Sc}, which arises as a consequence of a conforma-

*Address correspondence to this author at the Infectiologie Animale et Santé Publique, Institut National de la Recherche Agronomique, 37380 Nouzilly, France; Tel: 33 2 47 42 78 87; Fax: 33 2 47 42 77 79;
E-mail: nandi@tours.inra.fr

1389-5575/08 $55.00+.00

Box 1 Key findings in prion prtein-nucleic acid interaction

1962 Scrapie agent is resistant to ultra violet and ionising radiation and hence devoid of nucleic acid [1].
1982 Isolation of an infectious protease resistant glycoprotein from infected brain which occasionally formed amyloid deposits in the form of filamentous structures or rods[3].
1999 Polymerization of recombinant prion protein to protease resistant protein oligomers and amyloid polymers by synthetic DNA [31].
2001 Demonstration of DNA induced PrP^{Sc} secondary structure from recombinant prion protein and catalytic action of the protein-DNA complex on PrP^{Sc} conversion [34].
2001 Recombinant PrP^{C} condenses nucleic acids which formed functionally active nucleoprotein complex similar to functional retroviral nucleoprotein complex and mediates DNA strand transfer [53, 56, 57].
2002 Nucleic acid induced unfolding of the globular (α-helical) structure of prion protein induces polymerisation of prion protein to amyloid [36].
2003 Endogenous RNA was shown to convert endogenous PrP^{C} to PrP^{Sc} in vitro [37].
2003 Characterization of RNA aptamers which prevented prion protein polymerisation [43].
2004 DNA interaction with recombinant prion protein produced spherical amyloids and amyloids of different morphologies similar to those found in infected scrapie and CJD brains [27].
2005 Generation of infectious scrapie prions *in vitro* from a mixture of normal and scrapie infected brain homogenates [15].
2006 Demonstration that DNA interaction with prion protein is mainly mediated through its globular structure [35].
2006 Antiscrapie activity of oligonucleotides [58].
2006 Demonstration of reversible nature of RNA-prion protein interaction [46].
2007 Prion protein was found to bend and unwind DNA suggesting a possible functional role of the protein [54].
2007 Endogenous polyamines can prevent polymerisation of the prion protein by nucleic acids suggesting the possibilities that these amines can be used for detection as well as therapeutic purposes for prion disease [48].
2007 *De novo* generation of native infectious prion from the interaction of PrPC with synthetic nucleic acid [40].
2007 Demonstration that prion protein has both high and low affinity DNA binding sites [47].
2007 Selective incorporation of nucleic acid into *de novo* generated prions [41].

tional change of non-infectious monomeric α-helical soluble glycosylated cellular prion protein, PrP^{C} attached to the outer cell membrane through a glycophosphatidyl inositol linkage [3, 10]. The biological function of PrP^{C} remains largely unknown but the results suggested that the protein can play a role in maintaining cellular copper concentration, signal transduction, RNA binding and DNA metabolism [11]. PrP^{Sc} can exist as oligomers and amyloid polymers and unlike PrP^{C} is resistant to ProteinaseK(PK) digestion [3, 10]. The maximum prion infectivity has been found to be associated with prion particles (oligomers) having 17-27 nm diameter (300-600 kDa) whereas the large fibrils show lower prion infectivity [10]. The existence of multiple prion strains has also been attributed to the conformational variations of PrP^{Sc} [3]. Propagation of the disease has been considered to arise from the conversion of PrP^{C} by PrP^{Sc} to its like. Naturally occurring prion amyloid is constituted from 90-231 amino acid fragment of the full-length prion protein having 23-231 amino acids [3].

Amyloids obtained from the full-length hamster brain cellular PrP^{C} or *in vivo* isolated hamster PrP 27-30 amyloid have been found to be non-infectious in experimental animals over-expressing prion proteins [12]. However, amyloid formed from the truncated 90-231 fragment of mouse recombinant prion protein is found to be infectious and shows strain specificity of the prion disease in the experimental mice over-expressing this protein fragment but show very low levels of infectivity (less than 10^{8}-fold than bona fide PrP^{Sc}) when injected in wild mice suggesting the possibility that animals over-expressing prion protein were making prion spontaneously [10, 13, 14]. Inoculation of wild-type hamsters with *in vitro*-generated PK-resistant prion protein form by protein misfolding cyclic amplification in a cell free system (brain homogenate) has been found to be infectious which however also does not establish critically that the infectious agent in prion disease is composed of only protein since other molecules present in the brain homogenate may act as a cofactor for the observed results [10, 15]. From all these considerations, the involvement of host derived molecule viz. nucleic acids or sulphated glycosoaminoglycans as a cofactor for the conversion of PrP^{C} to PrP^{Sc} has not been ruled out [10].

SITES OF CONVERSION OF THE NORMAL PROTEIN TO DISEASED PROTEIN FORM

The sub-cellular site of the change in the conformation of PrP^{C} to PrP^{Sc} is not known with certainty and the structural change can occur at the cell surface or in the endosomes after internalisation [16-18]. However, prion protein has been demonstrated to be present in the cytoplasm [19-25]. Internalisation of PrP^{C} in neuronal cells in the presence of copper ions shows that the protein is present in the perinuclear compartment [20]. Prion protein has been found to be translocated to the nuclei of infected cells and interacts with chromatin [22]. It has been recently shown that that full-length prion protein without the GPI anchor accumulates in the nucleus of the hippocampal and neuroblastoma cell lines [23]. A mutant (D177N), which is associated with a heritable and transmissible form of the spongiform encephalopathy, has been shown to accumulate in the cytoplasm [24]. The evidence that PrP^{C} can exist in cytoplasm and interact with other molecules in there has been reported [25]. Thus, the prion protein has the possibility to interact with DNA/RNA present in the interior of the cell. It is possible that nucleic acid catalysed conversion of PrP^{C} to PrP^{Sc} in the cytoplasm produces oligomers and polymer amyloids related to prion infection [25, 26]. Morphological similarities between different types of amyloids formed from prion protein and nucleic acid interaction in solution and those found in cytoplasm of scrapie infected tissue further strengthens this suggestion [27].

NUCLEIC ACID INTERACTION WITH PRION PROTEIN

A great majority of the studies on the solution properties, structure and interaction with other molecules have been carried out with the unglycosylated recombinant prion protein, rPrP, expressed in *E. Coli*, which has been considered as a model for the cellular protein PrP^{C}. Human rPrP is a single domain basic protein (pI, 11) consisting of an extended N-terminal segment (residues 23-121) and a globular domain (residues 121-231) consisting of three α-helices that encompass residues 144–153 (helix 1), 172–194 (helix 2), and 200–227 (helix 3) and a short β-sheet formed by two strands at residues 129–131 and 161–163 [3, 10]. The unstructured N-terminal segment is highly basic, glycine rich and contains octapeptide residues where copper ions bind.

The first experimental evidence in solution that nucleic acid can bind with a segment of prion protein was provided by the interaction of synthetic nucleic acids with a prion peptide fragment 106-126 having the sequence KTNMKHMAGAAAAGAVVGGLG which has overall positive charge [28]. This synthetic peptide fragment was chosen since it shows neurotoxicity towards primary cultures of various rat brain cells [29]. Subsequently it was found that the above nucleic acids can induce polymerisation of the peptide to amyloids [30]. This prompted us to study the interaction of nucleic acids with the recombinant full-length 23-231 prion protein (rPrP) which lead to the demonstration that DNA can catalyse the conversion of rPrP into its amyloid which is resistant to PK-digestion [31]. It was further observed that the reaction of the protein either with double or single stranded nucleic acids produce amyloid fibril and fibres of different morphologies, similar to those identified in the prion diseased brains [27, 31]. In addition, the interaction also produced polymer lattices and spherical amyloids of different dimensions (15–150 nm in diameters) which have been found to be the most infectious polymeric structures of the protein [10, 27, 32]. The spherical amyloids structurally resemble "spherical particles" observed in natural spongiform encephalopathy and in scrapie-infected (TSE) brains [27].

At specific DNA to rPrP concentration ratios a conformational transition from predominantly α-helical structure of the protein PrP to a soluble β-sheet rich structure could be identified by circular dichroism [34]. Based on solution results, it has been suggested that host nucleic acid may modulate the balance between the cellular and the misfolded conformations by reducing the protein mobility and by making the protein-protein interactions more favourable. The absence of associated nucleic acid with the oligomeric and polymeric prion protein amyloids obtained from prion protein and nucleic acid interaction would suggest that these species dissociate from the nucleic acid after their formation [27]. There is no report yet whether prion protein oligomers and amyloid polymers obtained from nucleic acid interaction with the protein are toxic or infectious.

CHARACTERIZATION OF PrP-DNA COMPLEX

The structural characterization of the complex between prion protein with DNA has been carried out by using a small double-stranded 18 base pair oligonucleotide [35]. The small-angle X-ray scattering data show that the globular 121-231 domain of the protein (pI 7.2) dominates the formation of the complex although its binding constant (Kd ~ 500nM) to the olgonucleotide is comparable to that of the nucleotide with the full-length prion protein (pI 11.2). The nmr heteronuclear single-quantum coherence spectra data show that the changes in the protein spectra were clustered both in the globular segment and in the disordered region of the protein. The interaction between the oligonucleotide and nucleic acids both to the full-length protein and the globular protein fragment is dominated by electrostatic interaction [35]. Previously it was shown that the incubated mixture of the 121-231 fragment and nucleic acid yields amyloid fibres [36]. The secondary structure of the 121-231 amyloid formed in nucleic acid solution is similar to the *in vivo* isolated prion protein 27-30 amyloid but unlike in it, a hydrophobic milieu is absent in the 121-231-amyloid [36]. Thermal denaturation study demonstrates a partial unfolding of the 121-231 protein fragment in nucleic acid solution. It has been suggested that nucleic acid catalyses unfolding of prion protein helix 1, which is the most hydrophilic α-helix known among proteins, is responsible for the polymerization of the protein to amyloid [36].

RNA CAN AMPLIFY PrP^{SC} FROM ENDOGENOUS PrP^{C} *IN VITRO*

Deleault *et al.* from *in vitro* studies using brain tissue have provided strong evidence that nucleic acid can play a role in the conversion of PrP^{C} to the PK-resistant PrP^{Sc} in the presence of a cellular RNA of a molecular mass around 100 kDa (~300 nucleotides) which co-purified with ribosomal RNA [37]. These authors also observed that addition of RNA extracts from mouse or hamster tissues induced hamster PrP^{Sc} conversion whereas invertebrate RNA failed to support hamster PrP^{Sc} amplification, indicating species specificity of RNA in amplification of PrP^{SC}. The inability of endogenous DNA to amplify PrP^{Sc} formation observed by Deleault *et al.* is in variation from the solution results which showed that DNA by interacting with $rPrP^{C}$ produces PK resistant PrP-oligomers and amyloid fibres [37]. One explanation of this discrepancy can due to binding of DNA to its various ligands (viz. other DNA-binding proteins) in brain homogenate making it unavailable to interact with PrP^{C} [38].

A small highly structured RNA (197 nucleotides) which forms very stable nucleoprotein complexes with human recombinant prion protein and cellular PrP^{C} from various cell extracts and mammalian brain homogenates has been shown to produce PK-resistant protein indicating the formation of PrP^{Sc}. The results also showed that the activity of RNA manifests some species specificity since RNA from invertebrates did not show amplification [39]. The authors speculated that small non-coding RNAs which are abundant in the cell may be involved in PrP^{C} conversion *in vivo*.

FORMATION OF NATIVE PRIONS *IN VITRO*

Infectious prions *in vitro* was first generated by subjecting a mixture of normal and scrapie infected brain homogenates to protein misfolding cyclic amplification (PMCA) [40]. Recently by using this technique and using a nucleic acid synthetic poly(A) and hamster PrPC formation of de novo native and infectious prions has been achieved which has

been confirmed by bioassays in wild type hamsters [40]. This sample produced a unique regional profile characterized by relatively mild vacuolation in the frontal cortex and hippocampus, The study provides the first evidence that mammalian prions can be made by using biochemically well defined constituents native PrPC, and a synthetic nucleic acid. The requirement of an accessory nucleic acid suggests that endogenous nucleic acid cofactors may participate in prion propagation *in vivo*, by becoming selectively incorporated into complexes with prion protein molecules during the formation of native prions [41].

BINDING CHARACTERISTICS OF DIFFERENT NUCLEIC ACIDS WITH PrP

Binding of recombinant prion protein with DNA, tRNA and polyA, highly structured small RNAs, prokaryotic and eukaryotic prion protein mRNA pseudoknots, has been studied at cytoplasmic and endosomal pHs (pH 7 and 5 respectively). Thermodynamic analyses of the repeat region suggest the presence of several hairpin loop structures and a RNA pseudoknot in human prion mRNA. Computer generated three-dimensional structures of the human prion pseudoknot indicate prion protein and RNA interaction domains and the possible involvement of this interaction in prion protein (PrP^{C}) translation [42]. Reversible nature of prion protein interaction with RNA has also demonstrated [43-46].

The affinities (nanomolar range, see above) of the above nucleic acids for the prion protein and the number of sites (4-6, unpublished results) where the protein binds to the nucleic acids do not vary appreciably although the nucleic acids used have very different compositions and structures. The binding parameters do not depend upon pH of the solution and show a poor cooperativity. The reactants form larger nucleoprotein complexes at pH 5 compared to that at neutral pH. Electrostatic force between the protein and nucleic acids dominates the binding interaction at neutral pH (unpublished results). In contrast, nucleic acid interaction with the incipient nonpolar groups exposed from the structured region of the prion protein dominates the reaction at pH 5. Prion protein of a particular species forms larger complexes with prion protein mRNA pseudoknots of the same species. The three dimensional structure of the pseudoknots and not their base sequences probably dominates their interaction with prion protein (unpublished results). Binding studies of small ssDNA thioaptamers to PrP shows the existence of both high and low affinity binding affinities in PrP towards these DNAs [47].

NUCLEIC ACID APTAMERS

Research has been also focussed to find nucleic acid ligands which can have specific affinities for either PrP^{C} or PrP^{Sc} forms. Artificial RNA ligands or aptamers which bind specifically to infectious prions or scrapie associated fibrils or β-oligomeric form of prion protein have also been isolated from a number of mammalian species. 2'-fluoropyrimidine-substituted RNA aptamers bind selectively to disease-associated β-sheet-rich forms of the prion protein. These aptamers inhibit the accumulation of protease-resistant forms of PrP in a prion-seeded, *in vitro* conversion assay [44]. Conversely, certain DNA aptamers have been isolated which bind rPrP (α-form) with high affinity but not to the PrPSc form of the protein. These ligands show sequence and structure specificity when binding to rPrP. These nucleic acid aptamers have the potential to be used as both diagnostic or prophylactic tools [44].

MODULATION OF NUCLEIC ACID-PRION PROTEIN INTERACTION BY BIOLOGICALLY RELEVANT MOLECULES

As has been mentioned above, PrP^{C} can exist in cytoplasm where it can interact with other molecules, for example, with DNA/RNA present in the cytoplasm and catalyse the conversion of PrP^{C} to PrP^{Sc} producing oligomers and polymer amyloids causing the disease *in vivo*. It is conceivable that there would be some other molecules which would influence the above reaction and polymerisation of the protein since the prion disease is of relatively rare occurrence. Nucleic acids, both RNA and DNA, remain predominantly as complex with the biological polyamines, spermine and spermidine, in the cytoplasm [48]. These polyamines at their physiological concentrations can prevent polymerisation of the prion protein by nucleic acids and it can be surmised that nucleic acid induced polymerisation of PrP^{C} to PrP^{Sc} can occur when there will be a depletion of the concentrations of cytosolic polyamines [49]. Concentrations of the cellular polyamines are regulated by a complex circuitry of synthesis, degradation and cellular uptake and efflux [50]. The concentration of these amines in the cell can decrease either by gene disruption, defect in their biosynthesis or increased rate of break down [49-52]. It has been suggested that a decrease in polyamine concentrations in the cytoplasm due to the metabolic defects mentioned might trigger polymerisation of prion protein in the cytoplasm due to the availability of free nucleic acid to interact with PrP^{C}. Based on these observations we speculate that the polyamines can be used for diagnostic and therapeutic agent for prion disease [48].

CONFORMATIONAL CHANGES OF NUCLEIC ACID BY PRION PROTEIN

We have mostly described the changes in the conformation of prion protein by nucleic acids above. Study whether the same reaction induces conformational changes in the DNA has been also undertaken since prion protein accelerates DNA strand transfers process [53]. We have used biophysical methods to study DNA conformational change and electron microscopy to monitor the aggregation of the DNA molecules in the presence of prion protein.

Prion protein (rPrP) induced DNA conformational changes has been studied using oligonucleotides covalently labelled with energy donor fluorescein and acceptor rhodamine moieties by fluorescence resonance energy transfer (FRET). The protein induces strong FRET effect in the oligonucleotides evidenced from the simultaneous quenching of fluorescence intensity of the donor and increase in the fluorescence intensity of the acceptor which indicate bending of the oligonucleotides by prion protein. The protein also induces significant structural destabilization of the oligonucleotides evidenced from the lowering of their melting temperatures. The DNA structural changes observed in the presence of prion protein are similar to those caused by proteins involved in initiation and regulation of protein synthesis [54].

We have further observed that prion protein induces sequence specific condensation of DNA. The extent of condensation is maximum with the molecules containing the GC sequence where as the DNA containing AT sequences is not condensed by prion protein. The protein also induces greater exposure of the DNA bases to the bulk solvent in DNA containing GC bases (unpublished results). These results like the bending and unwinding of DNA by prion protein also suggests a biological function of the prion protein which needs to be explored. It is to be pointed out that the structured 121-231 segment of prion protein is unable either to bend or condense although the affinity constants (nanomolar range, see above) of the DNAs for the full-length 23-231 protein and the fragment are comparable [35, 54]. There are instances in the literature where protein induced DNA conformational change is independent of energetics of binding between the protein and DNA [55]. Our results show that that the N-terminal unstructured basic region of the protein is responsible for inducing DNA conformational changes.

Morphological studies by electron microscopy show that after relatively long incubation of prion protein and DNA mixture, ordered aggregation of the nucleic acid (protein-nucleic acid complex) resulted in small condensed spherical globules [56]. These small condensed globules further aggregated to larger globules. The nucleic acid globules are different from morphologically altered nucleic acid structures induced by other cellular DNA-binding proteins. Further, these large condensed nucleic acid globules dissociate spontaneously after very long period of incubation. The large condensed DNA structures resembled the human immunodeficiency virus (HIV-1) nucleocapsid protein NCp7 induced condensed globular aggregates of nucleic acids. In this system both the processes of condensation and dissociation of nucleoprotein complex are believed to be responsible for the functional properties of the above virus [56].

FUNCTIONAL PROPERTIES OF PrP-NUCLEIC ACID COMPLEX

The above similarities between the structural properties of the nucleoprotein complexes formed from NCp7 and prion protein and nucleic acids lead us to investigate the biological functional properties of PrP-nucleic acid complexes. The results show that the prion protein functionally resembles NCp7 of HIV-1. Like NCp7, prion protein accelerates the hybridization of complementary DNA strands and chaperone viral DNA synthesis during the minus and plus DNA strand transfers necessary to generate the long terminal repeats. The DNA-binding and strand transfer properties of the protein appear to map to the N-terminal fragment, whereas the structured C-terminal domain is inactive. These results suggest that PrP could be involved in nucleic acid metabolism *in vivo* [53]. Further, it has been also found that PrP has properties characteristic of NCp7 with respect to viral RNA dimerization and proviral DNA synthesis by reverse transcriptase [57]. The biological properties of PrP similar to the structural properties (bending, unwinding and condensation of DNA) map to the N-terminal region of the protein (see above). We suggest that both the changes in the prion protein and nucleic acid conformation would be relevant for prion infection.

THERAPEUTIC APPROACH

The uncertainties of the nature of the infectious agent and the mechanism of prion propagation have caused the development of effective therapy difficult [58]. Two types of therapies have been approached viz. immunotherapy and chemotherapy. The latter focuses on the conversion of PrP^{C} to the infection related PrP^{Sc} form. Polyanionic pentosan sulphate has been reported to increase the longevity of the vCJD patients. Various other compounds viz. porphyrins and phthalocyanins etc. have been effective in increasing the survival times of experimental rodents [59]. Degenerate single stranded phosphothioated analogues of nucleic acid at very low concentrations (nanomolar) inhibit PrP^{Sc} accumulation in cell culture and prolong the longevity of experimental mice [57, 58]. The effect of these analogues depend on their size, stereospecificity and hydrophobicity and not on their base compositions. The antiscrapie properties coupled with their anticoagulating activities, these phosphothioated nucleic acid analogues have been suggested to be more relevant compounds for the treatment of prion diseases than currently used pentosan sulphate [58].

CONCLUSION

Unlike in virus or bacteria where nucleic acid is the main infectious component for the propagation of the diseases, nucleic acid, among other polyanionic molecules, can induce oligomerization and polymerization of cellular prion protein which are considered as major components of the propagation of the prion disease. Concomitant changes in the nucleic acid conformations by prion protein are similar to those induced by nucleic acid regulatory proteins involved in gene expression. Further information in the above fields of the prion protein-nucleic acid interaction are expected to provide both biological functions of prion protein and prion infectivity.

ACKNOWLEDGEMENT

The work has been carried out from financial grants from GIS Prions and CEFIPRA.

REFERENCES

[1] Gajdusek, D.C.; Gibbs, C.J.; Alpers, M. *Nature,* **1966**, *209*, 794.
[2] Gibbs Jr. C.J.; Gajdusek, D.C.; Asher, D.M.; Alpers M.P.; Beck, E.; Daniel, P.M.; Mathews, W.B. *Science,* **1968**, *161*, 388.
[3] Prusiner, S. B. *Proc. Natl. Acad. Sci. USA*, **1998**, *95*, 13363.
[4] Alper, T.; Cramp, W.A.; Haig, D.A.; Clarke, M.C. *Nature,* **1967**, *214*, 764.
[5] Bolton, D.C.; McKinely, M.P.; Prusiner, S.B. *Science,* **1982**, *218*, 1309.
[6] Weissmann, C. *J. Biol.Chem*., **1999**, *274*, 3.
[7] Bruce, M.E.; Will, R.G.; Ironside, J.W.; McConnell, I.; Drummond, D.; Suttie, A.; McCardle, L.; Chree, A.; Hope, J.; Birket, C; Cousens, S.; Fraser, H.; Bostock, C.J. *Nature,* **1997**, *389*, 498.
[8] Wells, G.A.; Scott, A.C.; Johnson, C.T.; Gunning, R.F.; Hancock, R.D.; Jeffry, M.; Dawson, M.; Bradley, R. *Vet. Rec.,* **1987**, *121*, 419.
[9] Wroe, S.J.; Pal, S.; Siddique, D.; Hyare, H.; Macfarlane, S.; Joiner, S.; Linehan, J.M.; Brandner, S.; Wadsworth, J.D.; Hewit, P.; Collinge, J. *Lancet,* **2006**, *368*, 2061.
[10] Caughey, B.; Baron, G.S. *Nature,* **2006**, *443*, 803.
[11] Derrington, E.; Gabus, C.; Leblanc, C.; Chnaidermann; J.; Grave L.; Dormont, D.; Swietnicki, W.; Morillas, M.; Marc, D.; Nandi, P.; Darlix, P. *C R Biol*., **2002**, *325*, 17.
[12] Leffers, K-W.; Willie, H.; Stohr, J.; Junger, E.; Prusiner, S. B.; Riesner, D. *Biol. Chem*., **2005**, *386*, 569.

[13] Legname, G.; Baskakov, I. V.; Nguyen, H-O. B.; Riesner, D.; Cohen, F. E.; DeArmond, S.J.; Prusiner, S.B. *Science,* **2004**, *305*, 673.
[14] Legname, G.; Nguyen, H-O. B.; Baskakov, I. V.; Cohen, F.E.; DeArmond, S.J.; Prusiner, S.B. *Proc. Natl. Acad. Sci. USA,* **2005**, *102*, 2168.
[15] Castilla, J; Saa, P; Hetz, C; Soto, C. *Cell,* **2005**, *121*,195.
[16] Chesler, M. *Prog. Neurobiol.,* **1990**, *34*, 401.
[17] Caughey, B.; Raymond, G.J. *J. Biol. Chem.,* **1991**, *266,*18217.
[18] Borchelt, D.R.; Taraboulos, A.; Prusiner, S.B. *J. Biol. Chem.,* **1992**, *267*, 16188.
[19] Ma, J.; Wollmann, R.; Lindquist, S. *Science,* **2002**, *298*, 1781.
[20] Lee, K. S.; Magalhães, A. C.; Zanata, S. M.; Brentani, R.R.; Martin, V. R.; Zanata, S.M.; Brentani, R.R.; Martins, V.R.; Prado, M.A. *J. Neurochem.,* **2001**, *79*, 79.
[21] Mironov Jr., A.; Latawiec, D.; Wille, H.; Bouzamondo-Bernstein, E.; Legname, G.; Williamson, R.A.; Burton, D.; DeArmond, S.J.; Prusiner, S.B.; Peters, P.J. *J. Neurosci.,* **2003**, *23*, 7183.
[22] Mangé, A.; C. Crozet, S.; Lehmann S.; F. Béranger *J. Cell Sci.,* **2004**, *117*, 2411.
[23] Crozet, C.; Vezilier, J.; Delfieu, V.; Nishimura, T.; Onodera, T.; Casanova, D.; Lehman, S.; Béranger, F. *Mol. Cell Neurosci*., **2006**, *32*, 315.
[24] Ma, J.; Lindquist, S. *Proc. Natl. Acad. Sci. USA,* **2001**, *98,* 14955.
[25] Wang, X.; Wang, F; Arterburn, L.; Wollmann, R.; Ma, J. *J. Biol. Chem.,* **2006**, *281*, 13559.
[26] Nandi, P.K. *BioEssays,* **2004**, *26*, 469.
[27] Nandi, P.K.; Nicole. J.-C. *J. Mol. Biol.,* **2004**, *344*, 827.
[28] Nandi, P.K. *Arch. Virol.,* **1997**, *142*, 2537.
[29] Forloni, G.; Angeretti, G.; Chiesa, R.; Monzani, E.; Salmona M. Bugiani, O.; Tagliavini, F. *Nature,* **1993**, *362*, 543.
[30] Nandi, P.K. *Arch. Virol.,* **1998**, *143*, 1251.
[31] Nandi, P.K.; Leclerc, E. *Arch. Virol*., **1999**, *144*, 1751.
[32] Wille, H.; Michelitsch, M. D.; Guenebaut, V.; Supattapone, S.; Serban, A.; Cohen, F.E.; Agard, D.A.; Prusiner, S.B. *Proc. Natl Acad. Sci. USA,* **2002**, *99*, 3563.
[33] Vernon, M.L.; Horta-Barbosa, L.; Fuccillo, D. A.; Sever, J. L.; Baringer, J. R.; Bimbaum, G. *Lancet,* **1970**, *1*, 964.
[34] Cordeiro, Y.; Machado, F.; Juliano, L.; Juliano, M. A.; Brentani, R. R.; Foguel, D.; Silva, J.L. *J. Biol. Chem.,* **2001**, *276*, 49400.
[35] Lima, L.M.; Cordeiro, Y.; Tinoco, L.W.; Marques, A.F.; Oliveira, C.L.; Sampath, S.; Kodali, R.; Choi, G.; Foguel D.; Torriani, I.; Caughey, B.; Silva, J.L. *Biochemistry,* **2006**, *45*, 9180.
[36] Nandi, P.K.; Leclerc, E.; Nicole, J.C.; Takahashi M. *J Mol. Biol.,* **2002**, *322*,153.
[37] Deleault, N. R.; Lucassen, R.W.; Supattapone, S. *Nature,* **2003**, *425*, 717.
[38] Caughey, B.; Kocisko, D.A. *Nature,* **2003**, *425*, 673.
[39] Adler, V.; Zeiler, B.; Kryukov, V.; Kascsak, R.; Rubenstein, R.; Grossman, A. *J. Mol. Biol.,* **2003**, *332*, 47.
[40] Deleault, N.R.; Harris, B.T.; Rees, J.R.; Supattapone, S. (2007) *Proc. Natl. Acad. Sci. USA,* **2007**, *104*, 9741.
[41] Geoghegan, J.C.; Valdes, P.A.; Orem, N.R.; Deleault, N.R.; Williamson, R.A.; Harris, B.T.; Supattapone, S. *J. Biol. Chem.,* **2007**, *282*, 36341.
[42] Barrette, I.; Poisson, G.; Gendron, P.; Major, F. *Nucleic Acids Res.,* **2001**, *29*, 753.
[43] Rhie, A.; Kirby, L.; Sayer, N.; Wellesley, R.; Disterer, P., Sylvester, I.; Gill, A.; Hope, J.; James, W.; Tahiri-Alaoui. *J. Biol. Chem.,* **2003**, *278*, 39697.
[44] Takemura, K.; Wang, P.; Vorberg, I.; Surewicz, W.; Priola, S.A.; Kanthasamy, A.; Pottathil, R.; Chen, S.G.; Sreevatsan, S. *Exp. Biol. Med. (Maywood),* **2006**, *231*, 204.
[45] Watanabe, S.; Kusama-Eguchi, K.; Kobayashi, H.; Igarashi, K. *J. Biol. Chem.,* **1991**, *266*, 20803.
[46] Mercey, R; Lantier, I; Maurel, M.C.; Grosclaude, J; Lantier, F; Marc D. *Arch. Virol*., **2006**, *151*, 2197.
[47] King,D.J.; Safar, J.G.; Legname,G.; Prusiner,S.B. *J. Mol. Biol*., **2007**, *369*, 1001.
[48] Bera, A.; Nandi, P.K. *Arch. Virol.,* **2007**, 152, 655.
[49] Thomas, T.; Thomas, T.J. *Cell Mol. Life Sci.,* **2001**, *58*, 244.
[50] Childs, A.C.; Mehta, D.J.; Gerner, E.W. *Cell Mol Life Sci.,* **2003**, *60*, 1394.
[51] Igarashi, K.; Kashiwagi, K *Biochem. Biophys. Res. Commun.,* **2000**, *271,* 559.
[52] Seiler, N.; Raul, F. *J. Cell Mol. Med.,* **2005**, *9,* 623.
[53] Gabus, C.; Derrington, E.; Leblanc, P.; Chnaiderman, J.; Dormont D., Sweitnicki, W.; Morillas, M.; Surewicz, W.K.; Marc D.; Nandi, P.; Darlix, J.L. *J. Biol. Chem.,* **2001**, *276*, 19301.
[54] Bera, A.; Roche, A-C; Nandi P.K. *Biochemistry,* **2007**, 46,1320.
[55] Krishnamoorthy, G.; Roques, B.; Darlix, J.L.; Mely, Y. *Nucleic Acids Res.,* **2003**, *31*, 5425.
[56] Nandi, P.K.; Sizaret, P.Y. *Arch Virol*., **2001**, *146*, 327.
[57] Gabus, C; Auxellian, S.; Pechoux, C.; Dormont, D.; Sweitnicki, W.; Morillas, M.; Surewicz, W.K.; Nandi, P.; Darlix, J.L. *J. Mol. Biol.,* **2001**, *307*, 1011.
[58] Caughey, B.; Caughey, W.S.; Kocisco, D.A.; Lee, K.S., Silveira, J.R.; Morrey, J.D. *Acc. Chem. Res.,* **2006**, *39*, 646.
[59] Kocisko, D.A; Vaillant, A.; Lee K.S.; Arnold K.M.; Bartholet, N.; Race, R.E.; Olsen, E.A.; Juteau, J.M.; Caughey, B. *Antimicrob. Agents Chemother.,* **2006**, *50*,1034.

Received: 21 December, 2007 **Revised: 19 May, 2008** **Accepted: 20 May, 2008**