Recent Research Advances in the Glycine-xxx-Glycine Motif of Mammalian Prion Proteins

Jiapu Zhang*

School of Science, Informatics Technology and Engineering, Centre of Informatics and Applied Optimization, The Federation University of Australia, MT Helen Campus, Victoria 3353, Australia

Keywords: Prion protein; Glycine-xxx-Glycine motif; Recent research advances

Prion diseases such as Creutzfeldt–Jakob disease (CJD) in humans and bovine spongiform encephalopathy (‘mad-cow’ disease) in cattle are invariably fatal neurodegenerative diseases. Prions differ from conventional infectious agents in being highly resistant to treatments that destroy the nucleic acids found in bacteria and viruses. The infectious prion is thought to be an abnormally folded isoform (PrPSc) of a host protein known as the prion protein (PrPc). The highly conserved glycine-zipper region PrPc (119-131) of mammalian prion proteins, consisting of 3 repeats GAVGGLGGLGGMLG of the GxxxG protein-protein interaction motif (two glycines separated by any three residues), plays a crucial role in the formation or conversion of PrPSc from PrPC. This article will briefly review recent research advances in this motif.

This motif contains part of the β-sheet 1 (amino acids 128–131) and a PrPctm putative transmembrane domain (amino acids 112–135) [1,2]. A portion of the PrPc (118–135) exhibits a non-fibrillar property and in vivo cytotoxicity, and PrP amyloid formation may be associated with self-assembly by the GxxG motif of prion protein [2].

In 2006, Barnham et al. [1] reported both Aβ and PrP have three GxxG repeats, the crucial residue methionine (Aβ35, PrP129) located in the middle (GxMxG) of the last repeat, and disruption of GxxxG motifs will alter properties of Aβ and PrP [1]. In 2006, Choi et al. [2] generated a monoclonal antibody 1C5 (IgG1) recognized by the GxxG motif of PrPc.

In 2007, Harrison et al. [3] summarized the GxxGxPrPctm motif: “these motifs are commonly found in TM a-helices where they act to allow close packing and binding between helices. The GxxG motif of PrPc is highly conserved and antibodies raised against this region detect PrPc from many mammalian species. Both PrPc and β-amyloid peptide, causative agent of Alzheimer’s disease, contain this motif within regions that are capable of crossing the membrane, thus presenting a potential common mode of action for these two proteins which are both involved in neurodegenerative diseases” and pointed out “G131V disrupts one of the GxxG motifs found within the hydrophobic region, leading to the possibility that this motif may be relevant to the actions of TM-PrP”.

In 2010, Harrison et al. [4] reported that “mutagenesis studies demonstrate that minor alterations to this highly conserved region of PrPc (119-131) drastically affect the ability of cells to uptake and replicate prion infection in both cell and animal bioassay” and concluded that “these residues provide conformational flexibility”.

In 2013, Coleman et al. [5] studied mutations G114V and A117V and that the hydrophobic domain is an important determinant of PrP conversion”. From Figures 1 and 2, we know that, because of the mutations, the structure will unfolded / misfolded (“broken”) at

*Corresponding author: Jiapu Zhang, School of Science, Informatics Technology and Engineering, Centre of Informatics and Applied Optimization, The Federation University of Australia, MT Helen Campus, Victoria 3353, Australia, Tel: 423487360; E-mail: j.zhang@federation.edu.au

Received February 12, 2014; Accepted February 13, 2014; Published February 25, 2014


Copyright: © 2014 Zhang J. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
amino acids 114 and 117 respectively after 1 ns (where the molecular dynamics simulation condition is same as that of [6] and the PRESS, VOLUME (DENSITY) and RMSD were sufficiently stable to reach the equilibrations in the NPT systems). The A117V mutation breaks the strong hydrophobic core linkage ALA118-ALA117-ALA116-ALA115 (Figure 1) [6].

In conclusion, we might be able to say that the PrP glycine rich region GAVVGLGGYMLG can abrogate prion infection and it should be an important determinant of PrP conversion.

References


