Biochemistry & Pharmacology: Open Access

Zhang, Biochem Pharmacol 2014, 3:1
DOI: 10.4172/2167-0501.1000e151

Editorial Open Access

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

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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 (PrP^{Sc}) of a host protein known as the prion protein (PrP^{C}). The highly conserved glycine-zipper region PrP^{C} (119-131) of mammalian prion proteins, consisting of 3 repeats GAVVGGLGGYMLG of the GxxxG protein-protein interaction motif (two glycines separated by any three residues), plays a crucial role in the formation or conversion of PrP^{Sc} 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 PrP_{C} (118–135) exhibits a non-fibrillar property and *in vivo* cytotoxicity, and PrP amyloid formation may be associated with self-assembly by the GxxxG motif of prion protein [2].

In 2006, Barnham et al. [1] reported both Aβ and PrP have three GxxxG 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 GxxxG motif of PrP^{C}.

In 2007, Harrison et al. [3] summarized the GxxxG PrPctm motif: "these motifs are commonly found in TM a-helices where they act to allow close packing and binding between helices. The GxxxG motif of PrP is highly conserved and antibodies raised against this region detect PrP from many mammalian species. Both PrP 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 GxxxG motifs found within the hydrophobic region, leading to the possibility that this motif may be relevant to the actions of TM-PrP".

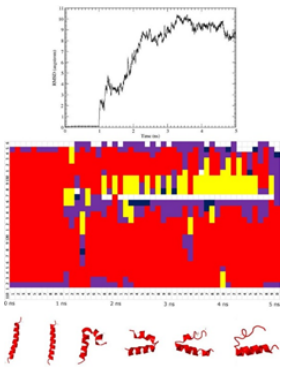

Figure 1: Human PrP(110-136) Mutant G114V. Variations of the root-mean-squared deviations (RMSD) from the optimized initial structure, the secondary structures, and the respective snapshots at 0 ns, 1 ns, 2 ns, 3 ns, 4 ns and 5 ns of the MD simulations for mutant G114V.

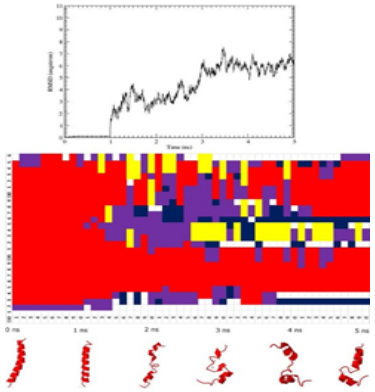

Figure 2: Human PrP(110-136) Mutant A117V. Variations of the root-mean-squared deviations (RMSD) from the optimized initial structure, the secondary structures, and the respective snapshots at 0 ns, 1 ns, 2 ns, 3 ns, 4 ns and 5 ns of the MD simulations for mutant A117V.

In 2010, Harrison et al. [4] reported that "mutagenesis studies demonstrate that minor alterations to this highly conserved region of PrP^{C} (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 lied before the glycine rich region of PrP^{C} (119-131) that can abrogate prion infection and concluded that "small, protease sensitive prion species have a significant role in the progression of prion disease 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

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

Citation: Zhang J (2014) Recent Research Advances in the Glycine-xxx-Glycine Motif of Mammalian Prion Proteins. Biochem Pharmacol 3: e151. doi:10.4172/2167-0501.1000e151

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 GAVVGGLGGYMLG can abrogate prion infection and it should be an important determinant of PrP conversion.

References

1. Barnham KJ, Cappai R, Beyreuther K, Masters CL, Hill AF (2006) Delineating common molecular mechanisms in Alzheimer's and prion diseases. Trends Biochem Sci 31: 465-472.
2. Choi JK, Park SJ, Jun YC, Oh JM, Jeong BH et al. (2006) Generation of monoclonal antibody recognized by the GXXXG motif (glycine zipper) of prion protein. Hybridoma 25: 271-277.
3. Harrison CF, Barnham KJ, Hill AF (2007) Neurotoxic species in prion disease: a role for PrP isoforms? J Neurochem 103: 1709-1720.
4. Harrison CF, Lawson VA, Coleman BM, Kim YS, Masters CLet al. (2010) Conservation of a glycine rich region in the prion protein is required for uptake of prion infectivity. J BiolChem 285: 20213-20223.
5. Coleman BM, Harrison CF, Guo B, Masters CL, Barnham KJ (2013) Pathogenic mutations within the hydrophobic domain of the prion protein lead to the formation of protease sensitive prion species with increased lethality. J Virol.
6. Zhang JP, Zhang YL (2013) Molecular dynamics studies on 3D structures of the hydrophobic region PrP(109-136). Acta Biochim Biophys Sin 45: 509-519.