

The Molecular Dynamics Simulation of Prion Protein

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1 Introduction

Transmissible spongiform encephalopathies (TSEs) are neurodegenerative diseases attributable to the structural transformation of cellular prion (PrPC) to its anomalous isoform (PrPSc). In humans, these diseases include kuru, Creutzfeldt-Jacob disease (CJD), fatal familial insomnia (FFI), and Gerstmann-Straussler-Scheinker syndrome (GSS), in sheep, scrapie, and in cattle, bovine spongiform encephalopathy (BSE). The most important aspect of prion diseases is the conformational transition of PrPC to PrPSc, both of which are isoforms with identical amino acid sequence. However, comparison of their secondary structures shows that PrPC is ~42% helical with a very low (~3%) β -sheet content, PrPSc, on the other hand, consists of 30% α -helices and 43% β -sheets. While the precise physiological role of PrPC, and the chemical difference between PrPC and PrP remain unknown, it appears that their differences are conformational.

The three-dimensional structures of monomeric PrPC from various sources have been determined by NMR spectroscopy and found to be very similar among many species. The N-terminal region (residues 23-124) is flexible, and the C-terminal region (residues 125-228) that contains the globular domains is well structured. All of these structures contain intramolecular disulfide bridges, three α -helices, and a short double-stranded β -sheet. Recent X-ray crystallographic studies determined the dimeric form of human PrPC. The dimer is the result of three-dimensional swapping of the C-terminal helix 3 and rearrangement of the disulfide bonds. The transition process from PrPC to PrPSc has been explained by two popular models. According to the hetero-dimer model, PrPSc induces the conformational change of PrPC by contact. The nucleation-dependent polymerization model of Lansbury and Caughey, on the other hand, suggests that PrPSc acts as a crystal seed at the starting point for crystal-like growth of a PrPSc oligomer and that conformational change occurs via transient interaction between PrPC and PrPSc. Several mutations in the primary structure of PrPC are known to segregate in variety of TSEs. In this study, we selected several mutations known to be associated with FFI. In these mutations, the change from a positively charged- to an uncharged residue may affect the hydrogen bonding network and

salt bridge. However, the function and dynamics of the PrPC remain to be elucidated.

2 Method and Results

Molecular dynamics (MD) simulations are widely used to simulate the motion of molecules in order to gain a deeper understanding of the chemical reactions, fluid flow, phase transitions, and other physical phenomena due to molecular interactions. Rapidly increasing computational power has made MD simulation a powerful tool for studying the structure and dynamics of biologically important molecules.

Most reported MD simulations of PrPC have been reported, involved short simulation times of less than 2 ns, or were performed using the AMBER ff94 force field, and most of the previously reported simulation targets were the C-terminal region which NMR determined. Higo et al. used the multi-canonical method to show that the ff96 force field reproduces the energy landscape more correctly than does the ff94 force field both in vacuo and in solvent water.

Our past simulation [1, 2] showed the necessity of simulation on N-terminal region to reveal the process that underlies the conformational transition from PrPC to PrPSc. We performed MD simulations on Wild Type and Mutant (Pro102Leu) of HuPrP90-231 at 300K. Pro102's phi value was very stable, remaining within a small range throughout our simulation. In contrast, Leu102's phi value varied considerably, allowing the possibility of interacting with other residues to form secondary structures, such as a beta sheet. This suggests that Pro102 is critical to prevent the transition from random structure to beta sheet structure in the wild type form.

References

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