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Molecular dynamics study on the conformational transition of prion induced by the point mutation: F198S

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Abstract

The single point mutation F198S in prion protein can induce aberrant 3-dimensional structure which finally lead to serious disease. One of the most significant differences between normal and abnormal structures is the concentration of α-helix and β-sheet. By employing molecular dynamics method, we studied the structural transition induced by the mutation F198S. Our results show that the loss of the hydrophobic interactions between the 198-th residue and its surroundings may lead to the transition. A creation of additional β-sheet is captured in our investigation which has not been reported in the dynamical studies of mutated induced structure conversion in prion protein.

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1. Introduction

Prion diseases, also known as Transmissible spongiform encephalopathies (TSEs), include Gerstmann–Straüssler–Scheinker syndrome (GSS), Creutzfeld–Jacob disease (CJD), fatal familial insomnia and kuru in human; bovine spongiform encephalopathy ("mad cow" disease) in cattle as well as sheep scrapie in sheep [1–3]. TSEs possess the features of viruses while the pathogen contains no nuclear acid, but only proteins. According to the famous "protein-only" hypothesis, the pathogen of TSEs is the aberrant isomer of prion protein (PrP^{Sc}). PrP^{Sc} is converted from the benign cellular isomer of prion protein (PrP^{C}) and could be accumulated. Finally, this accumulated PrP^{Sc} could degenerate the neural system [1–3]. Although many processes in pathology remain enigmas and different arguments are still in presence, more and more experimental discoveries support the doctrine. Therefore, attention has been focused on prion protein for diverse aims and by various methods [4–12].

PrP^{Sc} and PrP^{C} maintain the same primary structure. However they appear quite different in 3-Dimensional (3D) structures and chemical properties. The structure of a protein determines its functions. It is therefore natural that there would be disorder when the native structure of prion protein is crashed. X-ray diffractions and NMR both are effective experimental methods for capturing the 3D structures of proteins. By employing these tools, several features of proteins have been clarified. The native structure of prion protein has been obtained, see Fig. 1. And it shows that there are three α-helices and two short β-sheets in its native structure, instead of four α-helices as predicted by theoretical model [13,14]. These three α-helices are usually denoted as H1, H2 and H3 in literatures, respectively, from N-terminal to C-terminal. It may be different from PrP^{C}, PrP^{Sc} has different 3D structures and may be corresponding to different phenotypes of TSEs [3], instead of a uniform 3D structure. In despite of the 3D structure of PrP^{Sc} is not

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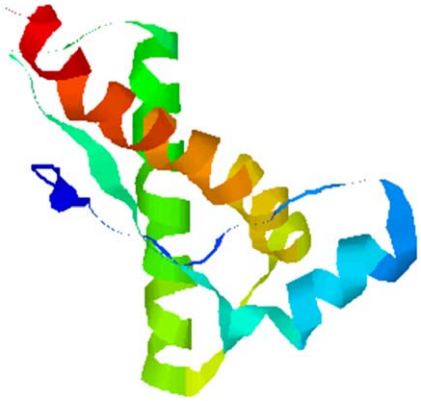

Fig. 1. According to the X-ray and NMR experimental results, there are three α-helices and 2 short β-sheets in the native structure of prion protein. Thus the structure is rich in α-helices and lack of β-sheets. What is shown is human prion protein structure whose PDB ID is 1HJM.

known so far. It has been revealed that the concentration of α-helix in PrP^{Sc} is lower than in PrP^{C} from experiments, e.g., circular dichroism (CD) spectrum. Meanwhile, the content of β-sheet is increased in PrP^{Sc} [15]. Furthermore, a recent plausible theoretical model predicted that there are only two α-helices remaining in PrP^{Sc}, H2 and H3 [16,17]. Except the forementioned features, biochemical experiments indicate that PrP^{C} is detergent soluble and protease sensitive. In contrast, PrP^{Sc} is insoluble in detergent and shows relatively resistant to protease [18,19]. It has been known that TSEs can occur sporadically, infectiously and genetically. Therein, GSS, familial CJD and fatal familial insomnia are dominantly inherited prion disease caused by mutations in the gene that codes the prion protein (PRNP) [1–3]. More than 20 different point mutations in PRNP which can induce TSEs were discovered experimentally [1–3]. It therefore suggests that some certain replacements of amino acid in prion protein will induce its conformation transition from PrP^{C} to PrP^{Sc}. Thereby, understanding the structural conversion initiated by point mutation is worthy of considerations. Actually, many Molecular Dynamics (MD) studies have been launched on the problem, e.g., on A117V, D178N, E200K, etc. [20–24]. All these works show the stability decreases after the mutation is introduced [20–24]. However, the creation of additional β-sheet is not observed. In the present work, we denote on the F198S mutation which would cause GSS. From our simulations, the creation of new β-sheet and the extension of the original β-sheet are shown clearly.

MD is applicable to study the structural conversion from PrP^{C} to PrP^{Sc}. However, it is a time-consuming task. Under the restriction of present computational ability, only a short period of time of dynamical behaviors can be explored. For the same reason, the number of atoms involved is limited. In a consideration of the restriction, MD is more suitable for investigation the dynamical properties of denature of proteins from native structure. It is impossible to capture the formation of PrP^{Sc} from PrP^{C} directly by MD simulation. However, it can provide the trend in configuration transformation. By employing these results, some interesting properties can be argued. Consequently, MD is a useful and a regular method in studying the issue, especially when there is lacking in more effective technique.

2. Simulations

The native structure which served as the initial structure of prion protein is obtained from Protein Data Bank (PDB). A human prion protein is selected whose PDB ID is 1HJM. Our simulations are carried out by GROMACS 3.1 [25,26]. The initial velocities of each atom are generated stochastically under the guarantee of Maxwell distribution. It is no doubt that the dynamical trajectory may be different when different initial velocities were adopted, especially at the beginning of the simulations. It is thus necessary to repeat the simulation for each sequence with various initial velocities to confirm the results. For each sequence, five different simulations are repeated, and the time is 10 ns in each simulation. In GROMACS, the different initial velocities are introduced by providing different seeds in pseudo random number generator. Each simulation costs about 50 CPU h in a computer configured as Intel 1.8 GHz CPU, 512 MB memory. In our simulation, the time step is 2 fs.

The native structure of wild type is set as the initial structure of mutated prion protein. Only the side chains of the 198th residues are modified to transform the amino acid from phenylalanine to serine. To avoid the modified atoms to be separated too far or too close, the structure is relaxed before simulation.

3. Results and discussions

α-helix is stabilized by the hydrogen bonds formed between the i-th CO groups and the $(i+4)$-th NH groups. The bound length will be never larger than 0.7 nm [20–22]. The distances between atoms can be observed conveniently in MD simulations. It is therefore enable us to track the changes in distance between the i-th CO groups and the $(i+4)$-th NH groups for checking out the formation and the crash of α-helix alone the period of simulation. This method is not only simple but also clear. Thus, many researchers have employed it in their works [20–22]. We will use this method in analyzing the dynamics of α-helix in the present paper as well. The stabilities of structures are usually quantitatively described by the Root Mean Square Distance (RMSD).

In Fig. 2, the stabilities of both wild type and F198S mutated prion protein are shown through RMSD data. Accordingly, the wild type is more stable than F198S prion protein. Furthermore, temperature disturbs the structure of F198S mutated prion protein heavily. Meanwhile, its influence in the structure of wild type is very small when temperature is ranged from 293 K to 310 K. The results are