Investigation on the Conformational Conversion of Human Prion Protein by Molecular Dynamics Simulation

Conformational conversion of α-rich cellular prion protein PrPC to its misfolded, β-rich and oligomeric counterpart PrPSc can cause fatal prion diseases. Despite numerous studies, the underlying mechanism for the β-enrichment during the conversion still remains elusive. By combining molecular dynamics (MD) simulations under different temperatures and pH values and simulated annealing simulation, the formation of a new β-strand, namely S3, was observed, leading to a stable three-stranded β-sheet structure in the PrP C-terminal domain. With a combination of polarizable structure-specific backbone charge (PSBC) model and replica exchange molecular dynamics (REMD) simulation, we simulated the folding of three N-terminal fragment peptides. Three new β-strands are found. By incrementally modeling the newfound β-strand onto the three-stranded β-sheet structure, we obtained a novel β-rich conformer with six-stranded antiparallel β-sheet spanning both the C-terminal domain and the N-terminal amyloidogenic region of PrP, which might serve as the β-core of the amyloid fibrils and can provide important insights into the mechanism of the conformational conversion of PrPC to PrPSc.

Date: 20 March 2017  
Time: 3.00 PM  
Venue: Conference Room, SPMS Level 2  
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