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The conformational transition of prion to β-strands in prion fibrillation from molecular dynamics simulations

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Abstract

Prion diseases, such as Creutzfeldt–Jakob disease, Gerstmann-Straussler-Scheinker syndrome, and fatal familial insomnia, are caused by the conversion of the cellular prion protein (PrPC) into an insoluble, beta-sheet-rich, infectious isoform (PrPSc) [1]. Structurally, this transformation involves the transition of the second and third α-helices in the prion C-terminal region into β-strands, which are stabilized by a disulfide bond in prion fibrils [2]. Through targeted molecular dynamics simulations, we identified critical regions in the prion sequence that initiate fibril formation under physiological conditions. Notably, regions 172-176, 190-200, and 220-224 showed early deformation and loss of structure during simulations. We also realized the prion C-terminal mutations disrupt hydrophobic interactions, destabilize electrostatic interactions and salt bridges, cause side-chain interference, or damage the hydrogen bond networks that enhance structural instability and promote amyloid fibril formation. This study provides molecular insights into the early stages of the prion fibrillation mechanism.

Keywords: α-β structural transition, Prion fibril formation, aggregation-prone sites, Targeted molecular dynamics simulation.

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