Mechanism of Unfolding of Human Prion Protein

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Abstract:

Misfolding and aggregation of prion protein are associated with several neurodegenerative diseases. Therefore, understanding the mechanism of the misfolding process is of enormous interest in the scientific community. It has been speculated and widely discussed that the native PrP^{C} form needs to undergo substantial unfolding to a more stable PrP^{C*} state, which may further oligomerize into the toxic scrapie (PrP^{Sc}) form.

Here we have studied the mechanism of unfolding of human prion protein (huPrP) using a set of extensive well-tempered metadynamics simulations. Through multiple microsecond-long metadynamics simulations, we find several possible unfolding pathways. We show that each pathway leads to an unfolded state of lower free energy than the native state. Thus, our study may point to the signature of a PrPC* form which corresponds to a global minimum on the conformational free energy landscape. Moreover, we find that these global minima states do not involve increased β-sheet content, as was assumed to be a signature of PrP^{Sc} formation in previous simulation studies. We have further analyzed the origin of metastability of the PrP^{C} form through free energy surfaces of the chopped helical segments to show that the helices, particularly H2 and H3 of the prion protein have the tendency to form either random coil or β-structure. Therefore, the secondary structural elements of the prion protein are only weakly stabilized by tertiary contacts and solvation forces so that relatively weak perturbations induced by temperature, pressure, pH, etc. can lead to substantial unfolding with characteristics of the intrinsically disordered proteins (IDP).