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Thermodynamic study at residue resolution of the unfolding and refolding process of H2H3 domain of prion protein

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Prion diseases are unique neurodegenerative diseases because their infectivity is mediated by the misfolding of the endogenous prion protein (PrP^{C}) towards the formation of a β-sheet-enriched and aggregated form (PrP^{SC}). PrP^{SC} has been observed as amyloid plaques in brains, and its formation arise from a structural rearrangement from the helical PrP^{C} to the pathological PrP^{SC}, which is able to template and promote the conformational change on other PrP^{C}. PrP^{C} contains an unstructured N-terminal tail and a folded C-terminal domain formed by three helices (H1, H2 and H3) and a short-stranded β-sheet (S1 and S2). The structure of PrP^{Sc} has not been elucidated yet, although for a long time it was accepted that the region S1H1S2 was crucial for the β-sheet seeding and the PrP^{SC} formation. However, in 2007 it was demonstrated that the fragment containing the helices H2H3 integrated the core of the amyloid fibrils. Later on, we proved that H2H3 fragment was: i) the only able to reproduce the oligomerization and the fibrilization pathways of PrP; ii) able to retain the native structure of PrP; and iii) able to interact with poly-lysine and avoid the cell infection. Hence, H2H3 could be the minimal region involved in the conformational change of PrP. Now we have done a step further trying to unveil the thermal unfolding/refolding pathways of H2H3. NMR spectroscopy revealed that folded and unfolded H2H3 display fast exchange equilibria. Moreover, 15N and $1H^{N}$ chemical shifts were used to derive the thermodynamic parameters at residue level. Unfolding of H2H3 starts at the N-terminus of H3, followed by the C-terminus of H2 and by the C-terminus of H3. The N-terminus of H2 is the region with higher stability. Unfolding/refolding occurs through the same pathway for most of the residues, although some of them show hysteresis (N177, H180 or A208).

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