Structural and Physiological Implications of Prion Protein Interaction with DNA

Millen, T. A.[2], Macedo, B.[1], Silva, P. F.[2], Gomes, M. P.[2] & Silva, J. L.[2], Cordeiro, Y.[1]

[1]Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil, 21941-902;
[2]Instituto de Bioquímica Médica, UFRJ, Rio de Janeiro, 21941-590, Brasil.

Prion diseases are neurodegenerative disorders caused by a pathogenic isoform of the prion protein, denominated PrP^{Sc}. This isoform is protease-resistant, forms amyloid fibrils and has high beta-sheet content. The cellular PrP (PrP^{C}), a highly conserved cell-surface glycoprotein, is protease-sensitive and has high alpha-helix content. The mechanisms involved in the PrP^{C} to PrP^{Sc} conversion are still unclear. Some studies suggest that this conversion can be assisted by another biological molecule. It has been proposed that the spontaneous conversion from PrP^{C} to PrP^{Sc} is prevented by a high energetic barrier and changes in the activation energy, like the presence of a catalyst, would lead to prion conversion. Among these ligands, nucleic acid molecules are putative candidates to participate in the PrP conversion. In the present work, we have investigated the interaction of recombinant PrP^{23-231} with double-stranded DNA oligonucleotides, through several spectroscopic techniques. We also aimed to characterize the thermodynamics of the PrP:DNA complex formation by isothermal titration calorimetry (ITC). Our ITC data show that these DNA sequences bind to PrP and this interaction induces immediate aggregation, confirmed by light scattering and tryptophan fluorescence measurements. Moreover, cell viability assays performed in neuroblastoma cell culture showed that some PrP:DNA aggregates are cytotoxic. Interestingly, not all DNA sequences induced formation of toxic PrP aggregates, suggesting that the nucleic acid sequence/structure is important for this process. In conclusion, the PrP:NA interactions can be the key for illumination of mechanisms involved in prion diseases, which affect humans and other mammals.
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