ABSTRACT

Identification of Key Nucleic Acid Determinants Involved in the Transcriptional Regulation of Prion Protein

Cellular prion protein (PrP^{C}) misfolds into an aberrant and infectious scrapie form (PrP^{Sc}) that manifests as fatal transmissible spongiform encephalopathies (TSEs). Association of prions with G-quadruplex (GQ) forming nucleic acid motifs is reported, but implications of this interaction remain elusive. Herein, the thesis show that the promoter region of the human prion gene (*PRNP*) contains two putative GQ motifs (Q1 and Q2) that assumes stable hybrid intra-molecular GQ structures. Both GQ motifs bind with high affinity to PrP^{C} but not to PrP^{Sc} like entities. Using a battery of techniques like SPR, fluorescence, NMR, CD and MD simulations combined with data from luciferase reporter assays and confocal microscopy it is shown that PrP^{C} auto-regulates its expression by binding and resolving the GQs present in its own promoter. Using truncated PrP mutants it is found that this resolvase-like activity is mediated by the protein's N-terminal region (residues 23- 89). Together, these results highlight a positive transcriptional feedback regulation of the *PRNP* gene by PrP^{C} through dynamic unwinding of GQs in its promoter, which gets annihilated by the formation of pathogenic PrP^{Sc}. Taken together, the findings of this thesis suggest that the loss of feedback regulation of the *PRNP* gene is a critical event in the pathogenesis of prion diseases.