ABSTRACT

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

Cellular prion protein (PrPC) misfolds into an aberrant and infectious scrapie form (PrPSc) 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 PrPC but not to PrPSc 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 PrPC 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 PrPC through dynamic unwinding of GQs in its promoter, which gets annihilated by the formation of pathogenic PrPSc. 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.