Non-Specific Prion Protein–Nucleic Acid Interactions Lead into Different Aggregates and Cytotoxic Species

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A misfolded form of the prion protein (PrP) is the primary culprit in mammalian prion diseases. It has been shown that nucleic acids catalyze the misfolding of the cellular PrP (PrPC) into a scrapie-like conformer (PrPSc). Also, it has been observed that interaction of PrP with nucleic acids is non-specific and that the complex can be toxic to cultured cells. No direct correlation has yet been drawn between changes in PrP structure and toxicity due to nucleic acid-binding. Here we asked whether different aggregation, stability, and toxicity effects are detected when non-related DNA sequences interact with recombinant PrP. Using spectroscopic techniques to analyze the PrP tertiary and secondary structure and cellular assays to check for toxicity, we found that rPrP:DNA interactions lead to different aggregated species depending on the DNA sequence tested. The 21-mer DNA sequence (D67) induced higher aggregation and also dissimilar structural changes of rPrP.. The rPrP:D67 complex induced major cell dysfunction, which appears to be correlated with the biophysical properties of the complex. Although sequence specificity is not apparent for PrP:nucleic acid interactions, we propose that particular nucleic acid patterns govern PrP recognition. The understanding of the structural and cellular effects observed for PrP:nucleic acid complexes may shed light on the still-mysterious pathology and physiology of the prion protein.

Word Keys: prion; nucleic acid; aggregation; spectroscopy; stability; protein-nucleic acid interaction.

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