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Protein Misfolding in Human Diseases

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Akademisk avhandling

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ABSTRACT

The studies in this thesis are focused on misfolded proteins involved in human disease. There are several well known diseases that are due to aberrant protein folding. These types of diseases can be divided into three main categories:

1. Loss-of-function diseases
2. Gain-of-toxic-function diseases
3. Infectious misfolding diseases

Most *loss-of-function diseases* are caused by aberrant folding of important proteins. These proteins often misfold due to inherited mutations. The rare disease carbonic anhydrase II deficiency syndrome (CADS) can manifest in carriers of point mutations in the human carbonic anhydrase II (HCA II) gene. One mutation associated with CADS entails the His107Tyr (H107Y) substitution. We have demonstrated that the H107Y mutation is a remarkably destabilizing mutation influencing the folding behavior of HCA II. A mutational survey of position H107 and a neighboring conserved position E117 has been performed entailing the mutants H107A, H107F, H107N, E117A and the double mutants H107A/E117A and H107N/E117A. We have also shown that the binding of specific ligands can stabilize the disease causing mutant, and shift the folding equilibrium towards the native state, providing a starting point for small molecule drugs for CADS.

The only known infectious misfolding diseases are the prion diseases. The human prion diseases Kuru, Gerstmann-Sträussler-Scheinker disease (GSS) and variant Creutzfeldt-Jakob are characterized by depositions of amyloid plaque from misfolded prion protein (HuPrP) in various regions of the brain depending on disease. Amyloidogenesis of HuPrP is hence strongly correlated with prion disease. Amyloid fibrillation and oligomer formation of PrP in *in vitro* studies have so far been performed under conditions where mild to harsh conditions of denaturants of various sorts have been included. In this work we show the unusual behavior of recombinant human prion protein during protein aggregation and fibrillation when performed under non-denaturing conditions close to physiological. We show that HuPrP amyloid fibrils are spun and woven from disordered aggregates.

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