

Poster Presentation

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Structural Basis of Prion Protein Conformation Conversion Inhibition

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Prion diseases are fatal neurodegenerative diseases that affect humans and other animals. A conformational transition of the cellular prion protein, Pr^{PC}, into an infectious isoform, Pr^{Sc}, is the central event leading to aggregation and the fatal progression of these diseases. One of the therapeutic approaches for the prion diseases is the use of pharmacological chaperones. These molecules can stabilize the prion protein in its native conformation and can arrest the disease progression. Tricyclic phenothiazine compounds exhibit anti-prion activity; however, the underlying molecular mechanism of Pr^{Sc} inhibition remains elusive. We have determined the molecular structures of promazine and chlorpromazine bound to the mouse prion protein (moPrP) by forming crystals of the ternary complexes of the POM1 Fab:moPrP:promazine and the POM1 Fab:moPrP:chlorpromazine. The structures were solved by X-ray crystallography to resolutions of 1.9 Å and 2.2 Å, respectively. The small molecules are bound in a novel binding pocket formed at the intersection of the structured and the unstructured domains of the moPrP. Promazine binding induces a structural rearrangement of a portion of the unstructured region proximal to the first β -strand, β 1, through the formation of a “hydrophobic anchor”. We demonstrate that these molecules, promazine in particular, allosterically stabilize the misfolding initiator-motifs such as C-terminus of helix, α 2, the α 2- α 3 loop as well as the polymorphic β 2- α 2 loop. Hence, the stabilization effects of the phenothiazine derivatives on initiator-motifs, induce a Pr^{PC} isoform that potentially resists oligomerization. Subtle structural differences are observed in the so-called initiator-motifs of the prion proteins that belong to many different mammalian species, and these diversities may possibly explain the generation of wide variety of scrapie strains in prion diseases.

Keywords: Prion Protein, Phenothiazine compounds, Initiator Motifs