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Prions, From Structure to Epigenetics and Neuronal Functions[1]

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Prions are a unique type of protein that can misfold and convert other proteins to the same shape. The well-characterized yeast prion [PSI+] is formed from an inactive amyloid fiber conformation of the translation-termination factor, Sup35. This altered conformation is passed from mother cells to daughters, acting as a template to perpetuate the prion state and providing a mechanism of protein-based inheritance. We employed a variety of methods to determine the structure of Sup35 amyloid fibrils. First, using fluorescent tags and cross-linking we identified specific segments of the protein monomer that form intermolecular contacts in a "Head-to-Head," "Tail-to-Tail" fashion while a central region forms intramolecular contacts. Then, using peptide arrays we mapped the region responsible for the prion transmission barrier between two different yeast species. We have also used optical tweezers to reveal that the non-covalent intermolecular contacts between monomers are unusually strong, and maintain fibril integrity even under forces that partially unfold individual monomers and extend fibril length. Based on the handful of known yeast prion proteins we predicted sequences that could be responsible for prion-like amyloid folding. Our screen identified 19 new candidate prions, whose protein-folding properties and diverse cellular functions we have characterized using a combination of genetic and biochemical techniques. Prion-driven phenotypic diversity increases under stress, and can be amplified by the dynamic maturation of prion-initiating states. These qualities allow prions to act as "bet-hedging" devices that facilitate the adaptation of yeast to stressful environments, and might speed the evolution of new traits. Together with Kandel and Si, we have also found that a regulatory protein that plays an important role in synaptic plasticity behaves as a prion in yeast. Cytoplasmic polyAdenylation element binding protein, CPEB, maintains synapses by promoting the local translation of mRNAs. We postulate that the self-perpetuating folding of the prion domain acts as a molecular memory. Thus yeast prions have provided evidence for the surprising possibility that amyloid protein folds can serve as the basis for memory and inheritance.

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