Current Topics in Biophysics, 2007, 30 (suppl. B) 13

THE ENIGMA OF THE PRION: A BIOPHYSICAL PERSPECTIVE

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Transmissible spongiform encephalopathies (TSEs or prion diseases) represent a group of fatal neurodegenerative disorders which, like Alzheimer's and Parkinson's disease, are associated with accumulation of abnormal protein deposits, often composed of fibrillar amyloid. In the case of TSEs, these misfolded aggregates arise from a conformational conversion of the normally monomeric and α-helical prion protein, PrP^{C}, to the β-sheet rich PrP^{Sc}, the latter believed to constitute the infectious prion agent. Here, we explore fundamental aspects of prion propagation and transmissibility barriers using an *in vitro* model of seeded fibrillization of the C-truncated recombinant prion protein. Our data show that seeding specificity of PrP amyloids is determined not so much by sequence similarity per se but, rather, by fibril conformation. Amino acid sequence is important only insofar as it confers the preference for a particular fibril conformation *in a region that constitutes the "acceptor surface"* for PrP monomer. Amino acid substitutions outside this critical region have little effect on the seeding specificity, even if they affect the conformation of other parts of the prion protein. Furthermore, we demonstrate that cross-seeding between proteins from different species requires monomeric protein to be "adaptable" to the conformation of the amyloid seed. As a result of this adaptability, cross-seeding of PrP from species A with fibrils from species B may overcome natural sequence-based structural preferences, resulting in a new strain of amyloid A which inherits conformational properties and – by virtue of this – the seeding specificity of the template amyloid B. This conformational adaptation allows the newly emerged strain to cross transmissibility barriers that are impermeable to the original strain of the same protein. This lecture will also discuss new data on the molecular structure of human prion protein amyloid fibrils.